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(71) **Applicant** *(for all designated States except US)*: FUJISAWA PHARMACEUTICAL CO., LTD. [JP/JP]; 4-7, Doshomachi 3-chome, Chuo-ku, Osaka-shi, Osaka 541 (JP).

(72) **Inventors; and**

(75) **Inventors/Applicants** *(for US only)*: SAWADA, Kozo [JP/JP]; 1-4-3-602-301, Azuma, Tsukuba-shi, Ibaraki 305 (JP). YATABE, Takumi [JP/JP]; 4-1-1-420-302, Namiki, Tsukuba-shi, Ibaraki 305 (JP). NOMURA, Chie [JP/JP]; 17-203, Mibuhigashifuchidacho, Nakagyo-ku, Kyoto-shi, Kyoto 604 (JP). OKU, Teruo [JP/JP]; 8-2, Midorigaoka, Tsukuba-shi, Ibaraki 305 (JP). TANAKA, Hirokazu [JP/JP]; 3-10-21, Hanayashiki Souen, Takarazuka-shi, Hyogo 665 (JP).

(74) **Agent:** SEKI, Hideo; Fujisawa Pharmaceutical Co., Ltd., Osaka Factory, 1-6, Kashima 2-chome, Yodogawa-ku, Osaka-shi, Osaka 532 (JP).

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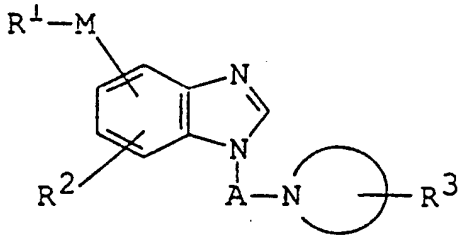
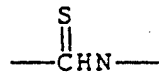
(54) **Title:** BENZIMIDAZOLE DERIVATIVES USEFUL AS DOPAMINE RECEPTOR ANTAGONIST, 5-HT RECEPTOR AGONIST OR α_1 RECEPTOR ANTAGONIST

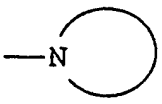
(57) **Abstract**



(I)



(a)



(b)

A benzimidazole compound of formula (I) in which R^1 is lower alkoxy, optionally substituted lower alkyl, cyclo(lower)alkyl, optionally substituted lower alkenyl, mono- or di(lower)alkylamino, optionally substituted heterocyclic group, or optionally substituted aryl, R^2 is hydrogen or lower alkyl, R^3 is optionally substituted aryl, A is lower alkylene, M is -NHCO-, -CONH-, (a), methylene or carbonyl, or R^1-M is amino, and formula (b) is N-containing heterocyclic group, or pharmaceutically acceptable salts thereof, which is useful as a dopamine receptor agonist, 5-HT receptor agonist or α_1 receptor antagonist.

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DESCRIPTION

BENZIMIDAZOLE DERIVATIVES USEFUL AS DOPAMINE RECEPTOR ANTAGONIST, 5-HT RECEPTOR AGONIST OR α 1 RECEPTOR ANTAGONIST

Technical Field:

The present invention relates to novel compounds and pharmaceutically acceptable salts thereof.

More particularly, it relates to novel benzimidazole derivatives and pharmaceutically acceptable salts thereof, which display effects on the peripheral or central nervous system, to processes for the preparation thereof, to a pharmaceutical composition comprising the same, to a use of the same as a medicament and to a method of the therapeutic treatment of diseases in a human being or an animal.

Accordingly, one object of the present invention is to provide novel benzimidazole derivatives and pharmaceutically acceptable salts thereof, which display effects on the peripheral or central nervous system, in particular on the peripheral nervous system.

Another object of the present invention is to provide processes for the preparation of novel benzimidazole derivatives and salts thereof.

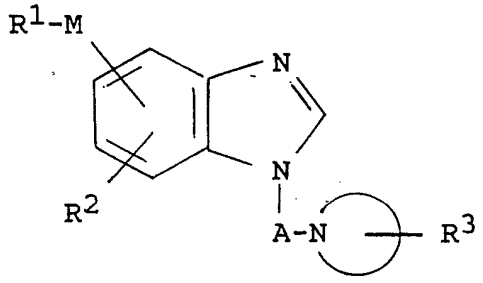
A further object of the present invention is to provide a pharmaceutical composition comprising, as an active ingredient, said benzimidazole derivatives and pharmaceutically acceptable salts thereof.

Still further object of the present invention is to

provide a use of said benzimidazole derivatives and pharmaceutically acceptable salts thereof as a dopamine receptor agonist; 5-HT receptor antagonist, especially 5-HT_2 receptor antagonist; α_1 receptor antagonist; and the like and a method of the therapeutic treatment of dopamine receptor mediated diseases; 5-HT receptor, especially 5-HT_2 receptor mediated diseases; α_1-receptor mediated diseases, particularly hypertension, cardiovascular disorder (e.g. angina pectoris, myocardial infarction, etc.), Parkinsonism, and the like, in a human being or an animal.

Disclosure of Invention:

The object benzimidazole derivatives are novel and can be represented by the following general formula :



(I)

in which R^1 is lower alkoxy, optionally substituted lower alkyl, cyclo(lower)alkyl, optionally substituted lower alkenyl, mono- or di(lower)alkylamino, optionally substituted heterocyclic group, or optionally substituted aryl,

R^2 is hydrogen or lower alkyl,

R^3 is optionally substituted aryl,

A is lower alkylene,

M is -NHCO-, -CONH-, -CHN-, methylene or carbonyl, or

R^1-M is amino, and

the formula :  is N-containing heterocyclic group,

or pharmaceutically acceptable salts thereof.

Suitable salts of the object compound (I) are pharmaceutically acceptable, conventional non-toxic salts and may include

a salt with a base such as an inorganic base salt, for example, an alkali metal salt (e.g. sodium salt, potassium salt, etc.), an alkaline earth metal salt (e.g. calcium salt, magnesium salt, etc.), an ammonium salt, an organic base salt, for example, an organic amine salt (e.g. triethylamine salt, pyridine salt, picoline salt, ethanolamine salt, triethanolamine salt, dicyclohexylamine salt, N,N'-dibenzylethylenediamine salt, etc.);

a salt with an acid such as inorganic acid addition salt (e.g. hydrochloride, hydrobromide, sulfate, phosphate, etc.), an organic acid addition salt (e.g. formate, acetate, trifluoroacetate, maleate, tartrate, fumarate, methanesulfonate, benzenesulfonate, etc.);
a salt with a basic or acidic amino acid (e.g. arginine, aspartic acid, glutamic acid, etc.); and the like.

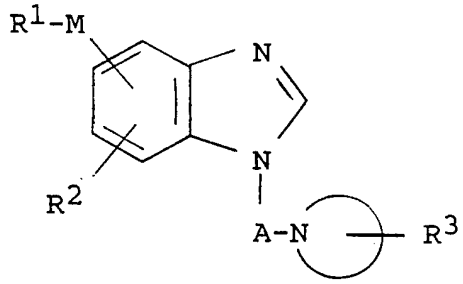
According to the present invention, the object compound (I) or pharmaceutically acceptable salts thereof can be prepared by the processes as illustrated by the following reaction schemes.

Process 1 :

(II)
or salts thereof

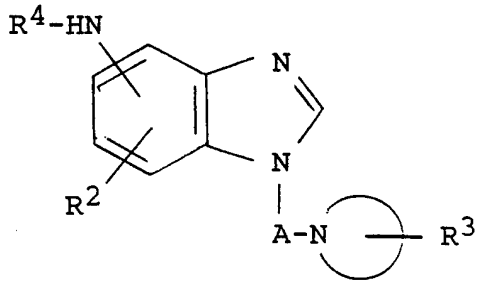
(III)

or salts thereof



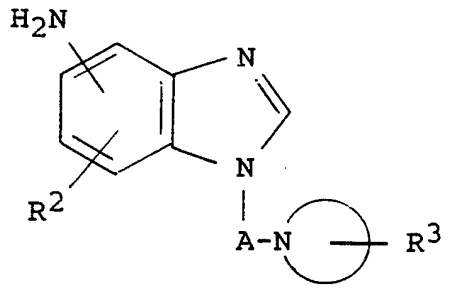
(I)
or salts thereof

Process 2 :



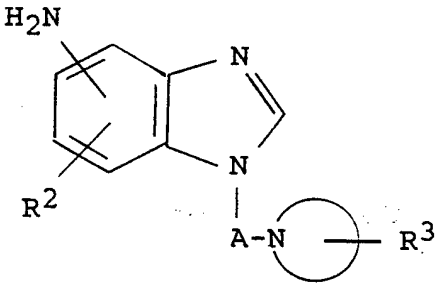
(IV)
or salts thereof

Removal of the common amino-protective group of R^4



(I-a)
or salts thereof

Process 3 :

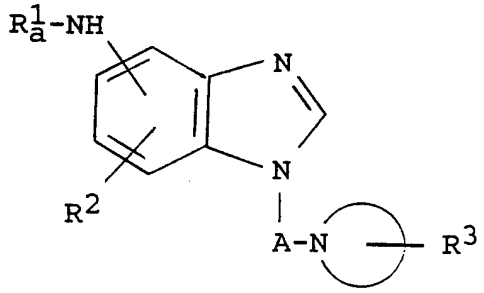


(I-a)
or a reactive derivative at the amino group, or salts thereof

R_a^1-OH

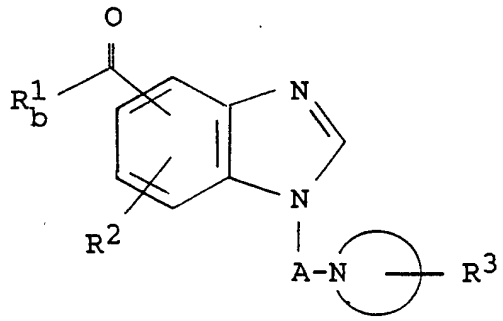
(V)

or a reactive derivative at the carboxy group, or salts thereof



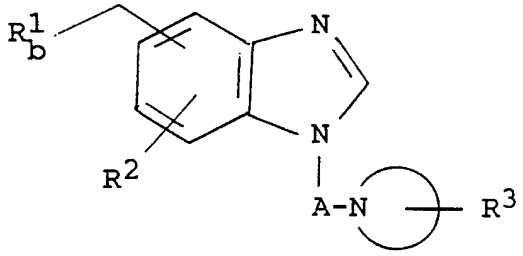
(I-b)
or salts thereof

Process 4 :



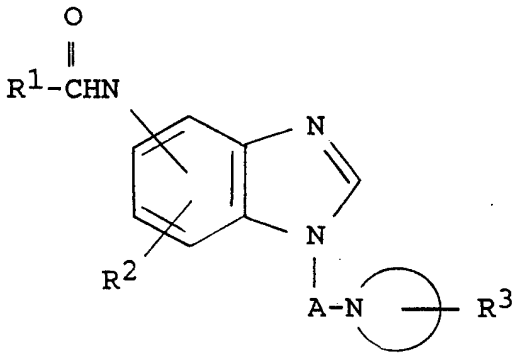
Reduction of the carboxy group

(I-c)
or salts thereof



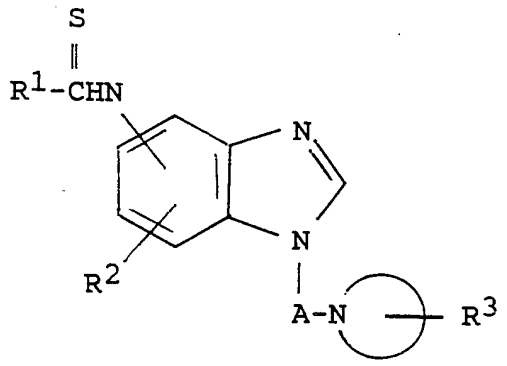
(I-d)
or salts thereof

Process 5



Lawesson's Reagent

(I-e)
or salts thereof



(I-f)

or salts thereof

in which R^1, R^2, R^3, A, M and the formula : -N◯ are each as defined above,

R^1_a is lower alkoxycarbonyl, lower alkanoyl, optionally substituted heterocyclic-carbonyl, mono- or di(lower)alkylcarbamoyl, lower alkoxy(lower)alkanoyl, optionally substituted aryloxy(lower)alkanoyl, cyclo(lower)alkylcarbonyl, cyclo(lower)alkyl(lower)alkanoyl, lower alkenoyl, aryl(lower)alkenoyl, optionally substituted arylcarbonyl, lower alkylthio(lower)alkanoyl, arylthio(lower)alkanoyl or arylamino(lower)alkanoyl,

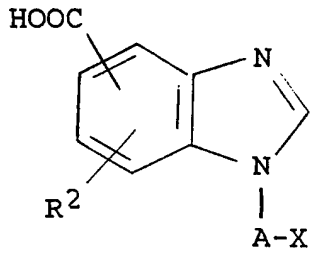
R^1_b is optionally substituted heterocyclic group, mono- or di(lower)alkylamino, or lower alkoxy,

R^4 is common amino-protective group, and

X is a leaving group.

The compound (II) used in the Process 1 may be new and can be prepared, for example, by the following methods or a conventional manner.

Method A :

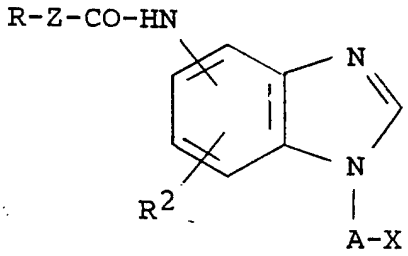


Curtius Rearrangement → [First Step]

R-Z-H (VII) → [Second Step]

(VI)

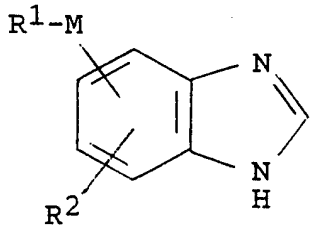
or a reactive derivative at the carboxy group, or salts thereof



(II-a)

or salts thereof

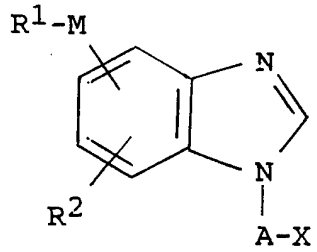
Method B :



X-A-Y (IX) →

(VIII)

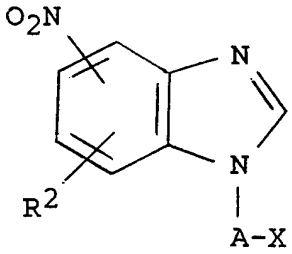
or salts thereof



(II)

or salts thereof

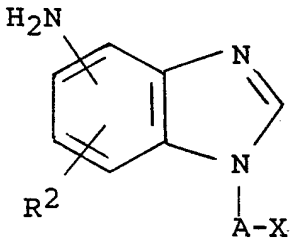
Method C :



Reduction of the nitro group

(X)

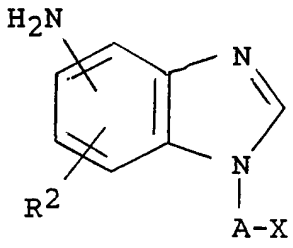
or salts thereof



(II-b)

or salts thereof

Method D :



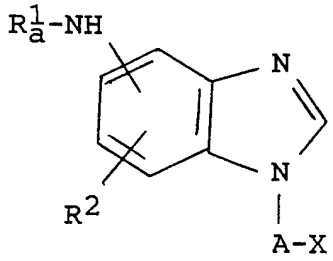
(II-b)

or a reactive derivative at the amino group, or salts thereof

R_a^1-OH

(V)

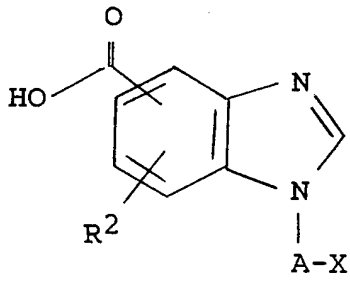
or a reactive derivative at the carboxy group, or salts thereof



(II-c)

or salts thereof

Method E

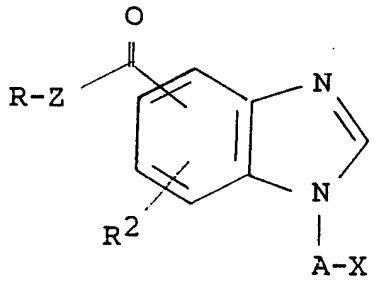


(VI)

or its reactive derivative at the carboxy group, or salt thereof

R-Z-H

(VII)



(II-d)

in which R^1, R^2, R^1_a, R^1_b, A, M and X are each as defined above,

Y is a leaving group,

Z is -O- or -NH-, and

the formula : R-Z-H means alcohols or amines.

In the above and subsequent descriptions of the present specification, suitable examples and illustrations of the various definitions which the present invention includes within the scope thereof are explained in detail as follows.

The term "lower" is intended to mean 1 to 6 carbon atom(s), preferably 1 to 4 carbon atom(s), unless otherwise indicated.

Suitable "lower alkoxy" may include straight or branched one such as methoxy, ethoxy, propoxy, isopropoxy, butoxy, t-butoxy, pentyloxy, hexyloxy, and the like, and the most preferable example may be ethoxy, isopropoxy and t-butoxy.

Suitable "optionally substituted lower alkyl" may include lower alkyl as mentioned below, lower alkoxy(lower)alkyl as mentioned below, optionally substituted aryloxy(lower)alkyl as mentioned below, cyclo(lower)alkyl(lower)alkyl as mentioned below, lower alkylthio(lower)alkyl as mentioned below,

arylthio(lower)alkyl as mentioned below, arylamino(lower)alkyl as mentioned below, aryl(lower)alkyl as mentioned below, heterocyclic-(lower)alkyl as mentioned below, or the like.

Suitable "lower alkyl" may include straight or branched one such as methyl, ethyl, propyl, isopropyl, butyl, t-butyl, pentyl, hexyl, and the like, and the most preferable example may be methyl for R^2, methyl, ethyl propyl and isopropyl for R^1.

Preferable "lower alkoxy(lower)alkyl" means aforementioned lower alkyl substituted by aforementioned lower alkoxy, in which the most preferable example may be methoxymethyl.

Preferable "optionally substituted aryloxy(lower)alkyl" means aforementioned lower alkyl substituted by aryloxy group such as phenoxy, tolyloxy, xylyloxy, cumenyloxy, mesityloxy, naphthyloxy, and the like, and said aryloxy group is optionally substituted by the group consisting of halogen as mentioned below, lower alkoxy as mentioned above, cyano, lower alkyl as mentioned above and halo(lower)alkyl as mentioned below, in which more preferable example may be phenoxy(lower)alkyl, mono- or dihalophenoxy(lower)alkyl, lower alkoxyphenoxy(lower)alkyl, cyanophenoxy(lower)alkyl, lower alkylphenoxy(lower)alkyl and [trihalo(lower)alkyl]phenoxy(lower)alkyl, and the most preferable one may be phenoxymethyl, 4-fluoro(or 4-bromo- or 3,4-dichloro)phenoxymethyl, 4-(or 2-)methoxyphenoxy-methyl, 4-cyanophenoxymethyl, 4-(or 3-)methylphenoxy-methyl, and 4-(trifluoromethyl)phenoxymethyl.

Preferable "halogen" may include fluorine, bromine, chlorine and iodine, in which more preferable example may be fluorine, bromine and chlorine.

Preferable "cyclo(lower)alkyl(lower)alkyl" means aforementioned lower alkyl substituted by

cyclo(lower)alkyl as mentioned below, in which the most preferable example may be cyclopentylmethyl.

Preferable "arylthio(lower)alkyl" means aforementioned lower alkyl substituted by arylthio group such as phenylthio, tolylthio, xylylthio, cumenylthio, mesitylthio, naphthylthio, and the like, in which the most preferable example may be phenylthiomethyl.

Preferable "arylamino(lower)alkyl" means aforementioned lower alkyl substituted by arylamino group such as phenylamino, tolylamino, xylylamino, cumenylamino, mesitylamino, naphthylamino, and the like, in which the most preferable example may be phenylaminomethyl.

Preferable "aryl(lower)alkyl" means aforementioned lower alkyl substituted by aryl as mentioned below, in which the most preferable example may be benzyl.

Preferable "heterocyclic-(lower)alkyl" means aforementioned lower alkyl substituted by heterocyclic group as mentioned below, in which more preferable example may be lower alkyl substitued by unsaturated 3 to 8-membered, preferably 5- or 6-membered heteromonocyclic group containing 1 to 4 oxygen atom(s), and the most preferable example may be 2-furylmethyl.

Preferable "halo(lower)alkyl" means aforementioned lower alkyl substituted by one or more, preferably one to three halogen, in which more preferable example may be trihalo(lower)alkyl, and the most preferable one may be trifluoromethyl.

Suitable "cyclo(lower)alkyl" may include cyclo(C_3-C_6)alkyl such as cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, and the like, in which the most preferable example may be cyclopropyl, cyclobutyl and cyclopentyl.

Suitable "optionally substituted lower alkenyl" may include lower alkenyl, aryl(lower)alkenyl, or the like.

Preferable "lower alkenyl" may include a conventional C_2-C_6 alkenyl such as vinyl, allyl, 1-(or 2-)methylvinyl,

propenyl, butenyl, pentenyl, hexenyl, and the like, in which the most preferable example may be vinyl, 1-(or 2-)-methylvinyl.

Preferable "aryl(lower)alkenyl" means aforementioned lower alkenyl substituted by aryl group as mentioned below, in which more preferable example may be phenyl(C_2-C_4)alkenyl, and the most preferable one may be 2-phenylvinyl.

Suitable "mono- or di(lower)alkylamino" means amino group substituted by one or two lower alkyl groups as mentioned above, in which more preferable example may be di(lower)akylamino and the most preferable one may be dimehtylamino.

Suitable "optionally substituted heterocyclic group" means heterocyclic group as mentioned below, which is optionally substitued by the group consisting of halogen as mentioned above, lower alkoxy as mentioned above, cyano, lower alkyl as mentioned above and halo(lower)alkyl as mentioned above, lower alkylthio as mentioned below, in which more preferable example may be;

unsaturated 3 to 8-membered (more preferably 5 or 6-membered) heteromonocyclic group containing 1 to 4 nitrogen atom(s),

saturated 3 to 8-membered (more preferably 5 or 6-membered) heteromonocyclic group containing 1 to 4 nitrogen atom(s),

saturated 3 to 8-membered (more preferably 5 or 6-membered) heteromonocyclic group containing 1 to 2 oxygen atom(s) and 1 to 3 nitrogen atom(s),

unsaturated 3 to 8-membered (more preferably 5 or 6-membered) heteromonocyclic group containing 1 to 2 sulfur atom(s) and 1 to 3 nitrogen atom(s),

unsaturated 3 to 8-membered (more preferably 5 or 6-membered) heteromonocyclic group containing 1 to 2 sulfur atom(s), and

unsaturated 3 to 8-membered (more preferably 5 or 6-membered) heteromonocyclic group containing an oxygen atom, each of which is optionally substituted by lower alkyl, and the like, wherein the most preferable one may be pyrazinyl, pyrimidinyl, pyrrolidinyl, piperidyl, piperazinyl, 4-methylpiperazinyl, morpholinyl, thiazolyl, thiadiazolyl, dihydrothiazolyl (e.g. 4,5-dihydrothiazolyl, etc.), furyl and thienyl.

Suitable "lower alkylthio(lower)alkyl" means aforementioned lower alkyl substituted by lower alkylthio as mentioned below, in which more preferable example may be C_1-C_4 alkylthio(C_1-C_4)alkyl, and the most preferable one may be methylthiomethyl.

Suitable "optionally substituted aryl" may include aryl as mentioned below, which is optionally substituted by one or more, preferably one or two substituent(s) such as halogen (e.g. fluorine, chlorine, bromine, iodine), lower alkyl as mentioned above (e.g. methyl, etc.), lower alkoxy (e.g. methoxy, etc.), and the like, in which more preferred example may be phenyl which is unsubstituted or substituted by lower alkoxy, and the most preferred one may be phenyl and 2-methoxyphenyl.

Preferable "aryl" may include C_6-C_{10} aryl such as phenyl, tolyl, xylyl, cumenyl, mesityl, naphthyl, etc.

Suitable "lower alkylthio" may include straight or branched one such as methylthio, ethylthio, propylthio, isopropylthio, butylthio, t-butylthio, pentylthio, hexylthio, and the like, and the most preferable example may be methylthio.

Suitable "common amino-protective group" may include mono or di or triphenylmethyl, acyl as mentioned below, in which said acyl group can be removed by a conventional removal reaction such as hydrolysis and reduction.

Suitable "acyl" may include aliphatic acyl, aromatic

acyl, heterocyclic acyl and aliphatic acyl substituted with aromatic or heterocyclic group(s) derived from carboxylic, carbonic, sulfonic and carbamic acids.

The aliphatic acyl may include saturated or unsaturated, acyclic or cyclic ones, for example, alkanoyl such as lower alkanoyl (e.g. formyl, acetyl, propionyl, butyryl, isobutyryl, valeryl, isovaleryl, pivaloyl, hexanoyl, etc.), alkylsulfonyl such as lower alkylsulfonyl (e.g. mesyl, ethylsulfonyl, propylsulfonyl, isopropylsulfonyl, butylsulfonyl, isobutylsulfonyl, pentylsulfonyl, hexylsulfonyl, etc.), carbamoyl, N-(or N,N-di)(lower)alkylcarbamoyl (e.g. methylcarbamoyl, ethylcarbamoyl, dimethylcarbamoyl, etc.), alkoxycarbonyl such as lower alkoxycarbonyl (e.g. methoxycarbonyl, ethoxycarbonyl, propoxycarbonyl, butoxycarbonyl, t-butoxycarbonyl, etc.), alkenyloxycarbonyl such as lower alkenyloxycarbonyl (e.g. vinyloxycarbonyl, allyloxycarbonyl, etc.), alkenoyl such as lower alkenoyl (e.g. acryloyl, methacryloyl, crotonoyl, etc.), cycloalkanecarbonyl such as cyclo(lower)alkanecarbonyl (e.g. cyclopropanecarbonyl, cyclobutanecarbonyl, cyclopentanecarbonyl, cyclohexanecarbonyl, etc.), and the like.

The aliphatic acyl substituted with aromatic group(s) may include aralkoxycarbonyl such as phenyl(lower)alkoxycarbonyl (e.g. benzyloxycarbonyl, phenethyloxycarbonyl, etc.), and the like.

The aromatic acyl may include aroyl (e.g. benzoyl, toluoyl, xyloyl, etc.), N-arylcarbamoyl (e.g. N-phenylcarbamoyl, N-tolylcarbamoyl, N-naphthylcarbamoyl, etc.), arenesulfonyl (e.g. benzenesulfonyl, tosyl, etc.), and the like.

The heterocyclic acyl may include heterocyclic-carbonyl and heterocyclic-carbamoyl, in which said heterocyclic group may include the heterocyclic group as

mentioned below,

in which more preferable examples may be furoyl, thenoyl, nicotinoyl, isonicotinoyl, thiazolylcarbonyl, thiadiazolylcarbonyl, morpholinylcarbonyl, tetrazolylcarbonyl, pyradinylcarbonyl, and the like.

The aliphatic acyl substituted with aromatic group(s) may include aralkanoyl such as phenyl(lower)alkanoyl (e.g. phenylacetyl, phenylpropionyl, phenylhexanoyl, etc.), aralkoxycarbonyl such as phenyl(lower)alkoxycarbonyl (e.g. benzyloxycarbonyl, phenethyloxycarbonyl, etc.), aryloxyalkanoyl such as phenoxy(lower)alkanoyl (e.g. phenoxyacetyl, phenoxypropionyl, etc.), and the like.

These acyl groups may be further substituted with one or more suitable substituents such as optionally substituted aryl, for example, phenyl optionally substituted by the group consisting of halogen (e.g. fluorine, bromine, chlorine, etc.), lower alkoxy (e.g. methoxy, etc), lower alkyl (e.g. methyl, etc.), cyano and mono- or di- or trihalo(lower)alkyl (e.g. trifluoromethyl, etc.); lower alkyl (e.g. methyl, ethyl, propyl, isopropyl, butyl, pentyl, hexyl, etc.); cyclo(lower)alkyl (e.g. cyclopentyl, etc.); halogen (e.g. chlorine, bromine, iodine, fluorine); lower alkoxy (e.g. methoxy, ethoxy, propoxy, isopropoxy, butoxy, pentyloxy, hexyloxy, etc.); lower alkylamino (e.g. methylamino, ethylamino, propylamino, isopropylamino, butylamino, pentylamino, hexylamino, etc.); arylamino (e.g. phenylamino, etc.); arylamino (e.g. phenylamino, etc.); nitro and the like.

Preferable "common protected amino" thus defined may be lower alkoxycarbonylamino and the most preferable one may be t-butoxycarbonylamino.

Suitable "lower alkylene" may include straight or branched one such as methylene, ethylene, trimethylene, tetramethylene, pentamethylene, hexamethylene, methylmethylene, ethylethylene, propylene, and the like,

in which the most preferred one may be tetramethylene.

Suitable "leaving group" may include imidazole, lower alkylimidazole (e.g. 2-methylimidazole, etc.), an acid residue such as halogen as mentioned above (e.g. chlorine, etc.), and the like.

Preferable "heterocyclic" moiety may include saturated or unsaturated, monocyclic or polycyclic heterocyclic group such as

unsaturated 3 to 8-membered (more preferably 5 to 7-membered) heteromonocyclic group containing 1 to 4 nitrogen atom(s), for example, azepinyl (e.g. 1H-azepinyl, etc.) pyrrolyl, pyrrolinyl, imidazolyl, pyrazolyl, pyridyl and its N-oxide, dihydropyridyl, pyrimidinyl, pyrazinyl, pyridazinyl, triazolyl (e.g. 4H-1,2,4-triazolyl, 1H-1,2,3-triazolyl, 2H-1,2,3-triazolyl, etc.), tetrazolyl (e.g. 1H-tetrazolyl, 2H-tetrazolyl, etc.) etc;

saturated 3 to 8-membered (more preferably 5 to 7 membered) heteromonocyclic group containing 1 to 4 nitrogen atom(s), for example, perhydroazepinyl (e.g. perhydro-1H-azepinyl, etc.) pyrrolidinyl, imidazolidinyl, piperidino, piperazinyl, etc;

unsaturated condensed heterocyclic group containing 1 to 4 nitrogen atom(s), for example, indolyl, isoindolyl, indolizinyl, benzimidazolyl, quinolyl, isoquinolyl, indazolyl, benzotriazolyl, etc;

saturated condensed heterocyclic group containing 1 to 4 nitrogen atom(s), for example, 7-azabicyclo[2.2.1]-heptyl, 3-azabicyclo[3.2.2]nonanyl, etc;

unsaturated 3 to 8-membered (more preferably 5 or 6-membered) heteromonocyclic group containing 1 to 2 oxygen atom(s) and 1 to 3 nitrogen atom(s), for example, oxazolyl, isoxazolyl, oxadiazolyl (e.g. 1,2,4-oxadiazolyl, 1,3,4-oxadiazolyl, 1,2,5-oxadiazolyl, etc.), etc;

saturated 3 to 8-membered (more preferably 5 or 6-

membered) heteromonocyclic group containing 1 to 2 oxygen atom(s) and 1 to 3 nitrogen atom(s), for example, morpholinyl, sydnonyl, etc;

unsaturated condensed heterocyclic group containing 1 to 2 oxygen atom(s) and 1 to 3 nitrogen atom(s), for example, benzoxazolyl, benzoxadiazolyl, etc;

unsaturated 3 to 8-membered (more preferably 5 or 6-membered) heteromonocyclic group containing 1 to 2 sulfur atom(s) and 1 to 3 nitrogen atom(s), for example, thiazolyl, isothiazolyl, thiadiazolyl (e.g. 1,2,3-thiadiazolyl, 1,2,4-thiadiazolyl, 1,3,4-thiadiazolyl, 1,2,5-thiadiazolyl, etc.), dihydrothiazinyl, etc;

saturated 3 to 8-membered (more preferably 5 or 6-membered) heteromonocyclic group containing 1 to 2 sulfur atom(s) and 1 to 3 nitrogen atom(s), for example, thiazolidinyl, etc;

unsaturated condensed heterocyclic group containing 1 to 2 sulfur atom(s) and 1 to 3 nitrogen atom(s), for example, benzothiazolyl, benzothiadiazolyl, etc;

saturated condensed heterocyclic group containing 1 to 4 nitrogen atom(s), and

saturated 3 to 8-membered heteromonocyclic group containing 1 to 2 oxygen atom(s) and 1 to 3 nitrogen atom(s),

unsaturated 3 to 8-membered (more preferably 5 or 6-membered) heteromonocyclic group containing an oxygen atom, for example, furyl, etc;

unsaturated 3 to 8-membered (more preferably 5 or 6-membered) heteromonocyclic group containing an oxygen atom and 1 to 2 sulfur atom(s), for example, dihydrooxathiinyl, etc;

unsaturated condensed heterocyclic group containing 1 to 2 sulfur atom(s), for example, benzothienyl, benzodithiinyl, etc;

unsaturated condensed heterocyclic group containing

an oxygen atom and 1 to 2 sulfur atom(s), for example, benzoxathiinyl, etc, and the like.

Suitable "N-containing heterocyclic group" means saturated or unsaturated, monocyclic or polycyclic heterocyclic group containing at least one nitrogen atom and optionally other hetero-atom(s) such as an oxygen, sulfur, nitrogen atom and the like, and said heterocyclic group is attached to A at the ring nitrogen atom.

Suitable N-containing heterocyclic group may be :

-unsaturated 3 to 8-membered, preferably 5- or 6-membered heteromonocyclic group containing 1 to 4 nitrogen atom(s), for example, pyrrol(-1-)yl, pyrrolin(-1-)yl, imidazol(-1-)yl, pyrazol(-1-)yl, tetrahydropyridin(-1-)yl [e.g. 1,2,3,6-tetrahydropyridin(-1-)yl, etc.], triazolyl [e.g. 4H-1,2,4-triazol(-4-)yl, 1H-1,2,3-triazol(-1-)yl, 2H-1,2,3-triazol(-2-)yl, etc.], tetrazolyl [e.g. 1H-tetrazol(-1-)yl, 2H-tetrazol(-2-)yl, etc.], dihydrotriazinyl [e.g. 4,5-dihydro-1,2,4-triazin(-4-)yl, 2,5-dihydro-1,2,4-triazin(-2-)yl, etc.], pyridyl, pyridazinyl, pyrimidinyl, pyrazinyl, tetrahydropyridyl [e.g. 1,2,3,6-tetrahydropyridin(-1-)yl, etc.], etc.;

-saturated 3 to 8-membered, preferably 5- or 6-membered heteromonocyclic group containing 1 to 4 nitrogen atom(s), for example, azetidin(-1-)yl, pyrrolidin(-1-)yl, imidazolidin(-1-)(or -3-)yl, piperidin(-1-)yl, pyrazolidin(-1-)yl, piperazin(-1-)yl, etc.;

-unsaturated 3 to 8-membered, preferably 5- or 6-membered heteromonocyclic group containing 1 to 2 oxygen atom(s) and 1 to 3 nitrogen atom(s), for example, oxazinyl [e.g. 4H-1,4-oxazin(-4-)yl, etc.], oxadiazinyl [e.g. 4H-1,2,4-oxadiazin(-4-)yl, etc.], etc.;

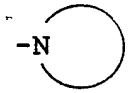
-saturated 3 to 8-membered, preferably 5- or 6-membered heteromonocyclic group containing 1 to 2 oxygen

atom(s) and 1 to 3 nitrogen atom(s), for example, morpholin(-4-)yl, etc.;

-unsaturated 3 to 8-membered, preferably 5- or 6-membered heteromonocyclic group containing 1 to 2 sulfur atom(s) and 1 to 3 nitrogen atom(s), for example, thiazolinyl [e.g. 1,3-thiazolin(-3-)yl, 1,2-thiazolin(-2-)yl, etc.], etc.;

-saturated 3 to 8-membered, preferably 5- or 6-membered heteromonocyclic group containing 1 to 2 sulfur atom(s) and 1 to 3 nitrogen atom(s), for example, thiazolidinyl [e.g. 1,3-thiazolidin(-3-)yl, 1,2-thiazolidin(-2-)yl, etc.], etc.;

wherein more preferred example may be saturated or unsaturated 5- or 6-membered heteromonocyclic group containing 1 to 4 nitrogen atom(s), and the most preferable one may be 1,2,3,6-tetrahydropyridin-1-yl.

One preferable embodiments of R^1, R^2, R^3, A, M and the formula  are as follows :

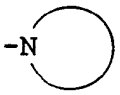
R^1-M is amino, lower alkanoylamino,
lower alkanethionylamino,
N,N-di(lower)alkylcarbamoylamino, lower alkoxycarbonylamino, lower alkenoylamino,
cyclo(lower)alkanecarbonylamino,
pyrazinylcarbonylamino, morpholinylcarbonylamino,
furylcarbonylamino, thienylcarbonylamino, lower alkoxy(lower)alkanoylamino,
cyclo(lower)alkyl(lower)alkanoylamino,
phenylamino(lower)alkanoylamino,
phenoxy(lower)alkanoylamino,
cyanophenoxy(lower)alkanoylamino, mono- or dihalophenoxy(lower)alkanoylamino,
trihalo(lower)alkylphenoxy(lower)alkanoylamino,

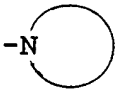
lower alkoxyphenoxy(lower)alkanoylamino,
lower alkylphenoxy(lower)alkanoylamino,
lower alkylthio(lower)alkanoylamino,
phenylthio(lower)alkanoylamino,
phenyl(lower)alkenoylamino, benzoylamino,
lower alkoxybenzoylamino, morpholinocarbonyl,
morpholinomethyl, pyrrolidinylcarbonyl,
pyrrolidinylmethyl, lower alkylpiperazinylcarbonyl,
N,N-di(lower)alkylcarbamoyl,
N,N-di(lower)alkylaminomethyl, lower alkoxycarbonyl,
piperidinocarbonyl, cyclo(lower)alkylcarbamoyl,
phenylcarbamoyl, pyrazinylcarbamoyl,
pyrimidinylcarbamoyl, thiazolylcarbamoyl,
thiadiazolylcarbamoyl, dihydrothiazolylcarbamoyl,
morpholinocarbamoyl, phenyl(lower)alkylcarbamoyl,
furyl(lower)alkylcarbamoyl,

R^2 is hydrogen or lower alkyl,

R^3 is phenyl which is unsubstituted or substituted by one to three substituent(s) selected from the group consisting of halogen and lower alkyl,

A is lower alkylene, and

the formula  is saturated or unsaturated 5- or 6-membered heteromonocyclic group containing 1 to 4 nitrogen atom(s) such as 1,2,3,6-tetrahydropyridin-1-yl, and the like.

Another preferable embodiments of R^1, R^2, R^3, A, M and the formula  are as follows :

R^1-M is amino, lower alkanoylamino, lower alkanethionylamino,
N,N-di(lower)alkylcarbamoylamino,

lower alkoxycarbonylamino, lower alkenoylamino, cyclo(lower)alkanecarbonylamino, pyrazinylcarbonylamino, morpholinylcarbonylamino, furylcarbonylamino, thienylcarbonylamino, thienylcarbonylamino optionally substituted by halogen, oxazolylcarbonylamino optionally substituted by lower alkyl, isooxazolylcarbonylamino optionally substituted by lower alkyl, pyrrolylcarbonylamino optionally substituted by lower alkyl, pyrazolylcarbonylamino, pyrimidinylcarbonylamino optionally substituted by the group consisting of lower alkoxy and lower alkylthio, lower alkoxy(lower)alkanoylamino, cyclo(lower)alkyl(lower)alkanoylamino, phenylamino(lower)alkanoylamino, phenoxy(lower)alkanoylamino, cyanophenoxy(lower)alkanoylamino, mono- or dihalophenoxy(lower)alkanoylamino, trihalo(lower)alkylphenoxy(lower)alkanoylamino, lower alkoxyphenoxy(lower)alkanoylamino, lower alkylphenoxy(lower)alkanoylamino, lower alkylthio(lower)alkanoylamino, phenylthio(lower)alkanoylamino, phenyl(lower)alkenoylamino, benzoylamino, lower alkoxybenzoylamino, morpholinocarbonyl, morpholinomethyl, pyrrolidinylcarbonyl, pyrrolidinylmethyl, piperazinylcarbonyl optionally substituted by lower alkyl, N,N-di(lower)-alkylcarbamoyl, N,N-di(lower)alkylaminomethyl, lower alkoxycarbonyl, piperidinocarbonyl, cyclo(lower)alkylcarbamoyl, phenylcarbamoyl, pyrazinylcarbamoyl, pyrimidinylcarbamoyl, thiazolylcarbamoyl, thiadiazolylcarbamoyl, dihydrothiazolylcarbamoyl, morpholinocarbamoyl, phenyl(lower)alkylcarbamoyl,

furyl(lower)alkylcarbamoyl,

R^2 is hydrogen or lower alkyl,

R^3 is phenyl which is unsubstituted or substituted by one to three substituent(s) selected from the group consisting of halogen and lower alkyl,

A is lower alkylene, and

the formula  is saturated or unsaturated 5- or 6-membered heteromonocyclic group containing 1 to 4 nitrogen atom(s) such as 1,2,3,6-tetrahydropyridin-1-yl, and the like.

The processes for the preparation of the object compound (I) of the present invention are explained in detail in the following.

(1) Process 1 :

The compound (I) or salts thereof can be prepared by reacting the compound (II) or salts thereof with the compound (III) or salts thereof.

Suitable salts of the compound (II) may be the same as those for the compound (I).

Suitable salts of the compound (III) may be the same acid addition salts such as those given for the compound (I).

The reaction is preferably carried out in the presence of alkali metal halide (e.g. sodium iodide, etc.).

This reaction is usually carried out in the presence of an inorganic base such as an alkali metal hydroxide (e.g. sodium hydroxide, potassium hydroxide, etc.), an alkaline earth metal hydroxide (e.g. magnesium hydroxide, calcium hydroxide, etc.), alkali metal hydride (e.g.

sodium hydride, potassium hydride, etc.), alkaline earth metal hydride (e.g. calcium hydride, etc.), alkali metal alkoxide (e.g. sodium methoxide, sodium ethoxide, potassium t-butoxide, etc.), an alkali metal carbonate (e.g. sodium carbonate, potassium carbonate, etc.), alkaline earth metal carbonate (e.g. magnesium carbonate, calcium carbonate, etc.), an alkali metal bicarbonate (e.g. sodium bicarbonate, potassium bicarbonate, etc.), etc.; an organic base such as trimethylamine, triethylamine, dicyclohexylamine, pyridine, picoline, lutidine, N-ethyl-N,N-diisopropylamine, etc.

This reaction can be carried out in a conventional solvent which does not adversely influence the reaction such as dichloromethane, pyridine, N,N-dimethylformamide, 4-methyl-2-pentanone, tetrahydrofuran, etc., or a mixture thereof.

The reaction temperature is not critical and the reaction is usually carried out under from warming to heating.

(2) Process 2 :

The compound (I-a) or salts thereof can be prepared by subjecting the compound (IV) or salts thereof to a removal reaction of the amino-protective group of R^4.

Suitable salts of the compounds (I-a) and (IV) may be the same as those for the compound (I).

The present reaction is usually carried out by a conventional method such as hydrolysis, reduction, and the like.

(i) Hydrolysis :

The hydrolysis is preferably carried out in the presence of a base or an acid. Preferable base may include an alkalimetal hydroxide (e.g. sodium hydroxide, potassium hydroxide, etc.), an alkaline earth metal

hydroxide (e.g. magnesium hydroxide, calcium hydroxide, etc.), alkali metal hydride (e.g. sodium hydride, potassium hydride, etc.), alkaline earth metal hydride (e.g. calcium hydride, etc.), alkali metal alkoxide (e.g. sodium methoxide, sodium ethoxide, potassium t-butoxide, etc.), an alkali metal carbonate (e.g. sodium carbonate, potassium carbonate, etc.), and alkaline earth metal carbonate (e.g. magnesium carbonate, calcium carbonate, etc.), an alkali metal bicarbonate (e.g. sodium bicarbonate, potassium bicarbonate, etc.), and the like.

Preferable acid may include an organic acid (e.g. formic acid, acetic acid, propionic acid, trifluoroacetic acid, benzenesulfonic acid, p-toluenesulfonic acid, etc.) and an inorganic acid (e.g. hydrochloric acid, hydrobromic acid, sulfuric acid, phosphoric acid, etc.). The acidic hydrolysis using trifluoroacetic acid is usually accelerated by addition of cation trapping agent (e.g. phenol, anisole, etc.).

This reaction is usually carried out in a conventional solvent which does not adversely influence the reaction such as water, dichloromethane, alcohol (e.g. methanol, ethanol, etc.), tetrahydrofuran, dioxane, acetone, etc., or a mixture thereof. A liquid base or acid can be also used as the solvent.

The reaction temperature is not critical and the reaction is usually carried out under from cooling to heating.

(ii) Reduction :

The reduction method applicable for this removal reaction may include, for example, reduction by using a combination of a metal (e.g. zinc, zinc amalgam, etc.) or a salt of chrome compound (e.g. chromous chloride, chromous acetate, etc.) and an organic or inorganic acid (e.g. acetic acid, propionic acid, hydrochloric acid,

sulfuric acid, etc.); and conventional catalytic reduction in the presence of a conventional metallic catalyst such as palladium catalysts (e.g. spongy palladium, palladium black, palladium oxide, palladium on carbon, colloidal palladium, palladium on barium sulfate, palladium on barium carbonate, palladium hydroxide or carbon, etc.), nickel catalysts (e.g. reduced nickel, nickel oxide, Raney nickel, etc.), platinum catalysts (e.g. platinum plate, spongy platinum, platinum black, colloidal platinum, platinum oxide, platinum wire, etc.), and the like.

In case that the catalytic reduction is applied, the reaction is preferably carried out around neutral condition.

This reaction is usually carried out in a conventional solvent which does not adversely influence the reaction such as water, alcohol (e.g. methanol, ethanol, propanoyl, etc.), dioxane, tetrahydrofuran, acetic acid, buffer solution (e.g. phosphate buffer, acetate buffer, etc.), and the like, or a mixture thereof.

The reaction temperature is not critical and the reaction is usually carried out under from cooling to warming.

(3) Process 3 :

The compound (I-b) or salts thereof can be prepared by reacting the compound (I-a) or a reactive derivative at the amino group, or salts thereof with the compound (V) or a reactive at the carboxy group or salts thereof.

Suitable salts of the compound (I-b) may be the same as those for the compound (I).

Suitable salts of the compound (V) may be salts with bases such as those for the compound (I).

Suitable reactive derivative at the carboxy group of the compound (V) may include an acid halide, an acid anhydride, an activated amide, an activated ester, and the

like. Suitable examples of the reactive derivatives may be an acid chloride; an acid azide; a mixed acid anhydride with acid such as substituted phosphoric acid [e.g. dialkylphosphoric acid, phenylphosphoric acid, diphenylphosphoric acid, dibenzylphosphoric acid, halogenated phosphoric acid, etc.], dialkylphosphorous acid, sulfurous acid, thiosulfuric acid, sulfuric acid, sulfonic acid [e.g. methanesulfonic acid, etc.], aliphatic carboxylic acid [e.g. acetic acid, propionic acid, butyric acid, isobutyric acid, pivalic acid, pentanoic acid, isopentanoic acid, 2-ethylbutyric acid, trichloroacetic acid, etc.] or aromatic carboxylic acid [e.g. benzoic acid, etc.]; a symmetrical acid anhydride; an activated amide with imidazole, 4-substituted imidazole, dimethylpyrazole, triazole or tetrazole; or an activated ester [e.g. cyanomethyl ester, methoxymethyl ester, dimethyliminiomethyl [$(CH_3)_2\overset{+}{N}=CH-$] ester, vinyl ester, propargyl ester, p-nitrophenyl ester, 2,4-dinitrophenyl ester, trichlorophenyl ester, pentachlorophenyl ester, mesylphenyl ester, phenylazophenyl ester, phenyl thioester, p-nitrophenyl thioester, p-cresyl thioester, carboxymethyl thioester, pyranyl ester, pyridyl ester, piperidyl ester, 8-quinolyl thioester, etc.], or an ester with a N-hydroxy compound [e.g. N,N-dimethylhydroxylamine, 1-hydroxy-2-(1H)-pyridone, N-hydroxysuccinimide, N-hydroxyphthalimide, 1-hydroxy-1H-benzotriazole, etc.], and the like. These reactive derivatives can optionally be selected from them according to the kind of the compound (V) to be used.

Suitable reactive derivative at the amino group of the compound (I-a) may include Schiff's base type imino or its tautomeric enamine type isomer formed by the reaction of the compound (I-a) with a carbonyl compound such as aldehyde, ketone or the like; a silyl derivative formed by the reaction of the compound (I-a) with a silyl compound

such as bis(trimethylsilyl)acetamide, mono(trimethylsilyl)acetamide, bis(trimethylsilyl)urea or the like; a derivative formed by reaction of the compound (I-a) with phosphorus trichloride or phosgene, and the like.

This reaction can be carried out in the presence of an organic or inorganic base such as alkali metal (e.g. lithium, sodium, potassium, etc.), alkaline earth metal (e.g. calcium, etc.), alkali metal hydride (e.g. sodium hydride, etc.), alkaline earth metal hydride (e.g. calcium hydride, etc.), alkali metal hydroxide (e.g. sodium hydroxide, potassium hydroxide, etc.), alkali metal carbonate (e.g. sodium carbonate, potassium carbonate, etc.), alkali metal bicarbonate (e.g. sodium bicarbonate, potassium bicarbonate, etc.), alkali metal alkoxide (e.g. sodium methoxide, sodium ethoxide, potassium tert-butoxide, etc.), alkali metal alkanoic acid (e.g. sodium acetate, etc.), trialkylamine (e.g. triethylamine, etc.), pyridine compound (e.g. pyridine, lutidine, picoline, 4-dimethylaminopyridine, etc.), quinoline, and the like.

In case that the compound (V) is used in a free form or its salt in this reaction, the reaction is preferably carried out in the presence of a condensing agent such as a carbodiimide compound [e.g. N,N'-dicyclohexylcarbodiimide, N-cyclohexyl-N'-(4-diethylaminocyclohexyl)carbodiimide, N,N'-diethylcarbodiimide, N,N'-diisopropylcarbodiimide, N-ethyl-N'-(3-dimethylaminopropyl)carbodiimide, etc.], a ketenimine compound (e.g. N,N'-carbonylbis-(2-methylimidazole), pentamethyleneketene-N-cyclohexylimine, diphenylketene-N-cyclohexylimine, etc.); an olefinic or acetylenic ether compounds (e.g. ethoxyacetylene, ß-chlorovinylethyl ether), a sulfonic

acid ester of N-hydroxybenzotriazole derivative [e.g. 1-(4-chlorobenzenesulfonyloxy)-6-chloro-1H-benzotriazole, etc.], a combination of trialkylphosphite or triphenylphosphine and carbon tetrachloride, disulfide or diazenedicarboxylate (e.g. diethyl diazenedicarboxylate, etc.), a phosphorus compound (e.g. ethyl polyphosphate, isopropyl polyphosphate, phosphoryl chloride, phosphorus trichloride, etc.), aminonyl chloride, oxalyl chloride, N-ethylbenzisoxazolium salt, N-ethyl-5-phenylisoxazolium-3-sulfonate, a reagent (referred to as so-called "Vilsmeier reagent") formed by the reaction of an amide compound such as N,N-di(lower)alkylformamide (e.g. dimethylformamide, etc.), N-methylformamide or the like with a halogen compound such as aminonyl chloride, phosphoryl chloride, phosgene or the like.

The reaction is usually carried out in a conventional solvent which does not adversely influence the reaction such as water, acetone, dichloromethane, alcohol (e.g. methanol, ethanol, etc.), tetrahydrofuran, pyridine, N,N-dimethylformamide, etc., or a mixture thereof.

The reaction temperature is not critical and the reaction is usually carried out under from cooling to heating.

(4) Process 4 :

The compound (I-d) or salts thereof can be prepared by reducing the carbonyl group of the compound (I-c) or salts thereof.

Suitable salts of the compounds (I-c) and (I-d) may be the same as those for the compound (I).

The methods of reduction and the reaction conditions (e.g. reaction temperature, solvent, etc.) are substantially the same as those illustrated in Process 2, and therefore are to be referred to said explanation, in which more preferable reduction method is lithium aluminum

hydride in tetrahydrofuran.

(5) Process 5 :

The compound (I-f) or salts thereof can be prepared by reacting the compound (I-e) or salts thereof with a Lawesson's Reagent.

Suitable salts of the compounds (I-e) and (I-f) may be the same as those for the compound (I).

The reaction is usually carried out in a conventional solvent which does not adversely influence the reaction such as water, acetone, dichloromethane, alcohol (e.g. methanol, ethanol, etc.), tetrahydrofuran, pyridine, dioxane, N,N-dimethylformamide, etc., or a mixture thereof.

The reaction temperature is not critical and the reaction is usually carried out under from warming to heating.

Methods A to E for preparing the new starting compound (II) or salts thereof are explained in detail in the following.

(A) Method A :

The compound (II-a) or salts thereof can be prepared by subjecting the compound (VI) or a reactive derivative at the carboxy group or salts thereof to a Curtius Rearrangement [First Step], and then reacting the resulting intermediate isocyanate compound with the compound (VII) [Second Step].

Preferable salts of the compound (VI) may be the same as those for the compound (I).

Preferable salts of the compound (II-a) may be the same as those for the compound (II).

[First Step]

Preferable reactive derivative at the carboxy group of the compound (VI) may include acid halide (e.g. acid chloride, etc.), acid hydrazide (i.e. $-CONH-NH_2$), and the like. In case that acid halide is used as the starting material, alkali metal azide (e.g. sodium azide, etc.) can be used as a reagent and in case that acid hydrazide is used as the starting material, nitrous acid and/or its alkali metal salt can be used as a reagent.

And in case that carboxylic acid per se is used as the starting material, a combination of alkali metal azide (e.g. sodium azide, etc.) and diarylphosphoryl azide (e.g. diphenylphosphoryl azide, etc.) or di(lower)alkylphosphoryl azide (e.g. diethylphosphoryl azide, etc.) can be used as a reagent [Modified Curtius Reaction, J. Am. Chem. Soc. 94, 6203, (1972)].

This reaction can be carried out in the presence of a base such as those mentioned in the explanation of Process 1.

This reaction can be carried out in a conventional solvent which does not adversely influence the reaction such as dichloromethane, pyridine, N,N-dimethylformamide, 4-methyl-2-pentanone, tetrahydrofuran, etc., or a mixture thereof.

The reaction temperature is not critical and the reaction is usually carried out under from warming to heating.

[Second Step]

This reaction can be carried out by reacting the intermediate isocyanate compound of First Step with the compound (VII).

Preferable examples of the compound (VII) may be alcohol such as methanol, ethanol, propanol, isopropyl alcohol, butanol, isobutanol, sec-butyl alcohol,

tert-butyl alcohol, pentanol, hexanol, etc., amine such as morpholine, dimethylamine, etc.

This reaction can be carried out in a conventional solvent which does not adversely influence the reaction such as dichloromethane, pyridine, N,N-dimethylformamide, 4-methyl-2-pentanone, tetrahydrofuran, etc., or a mixture thereof.

The reaction temperature is not critical and the reaction is usually carried out under from cooling to heating.

If the First Step was carried out in the presence of the compound (VII), these two steps can be carried out in one pot and can yield the compound (II-a) or salts thereof directly from the compound (VI) without isolating the intermediary isocyanate compound.

(B) Method B :

The compound (II) or salts thereof can be prepared by reacting the compound (VIII) or salts thereof with the compound (IX).

Preferable salts of the compound (VIII) may be the same as those for the compound (II).

This reaction can be carried out in the presence of a base such as those mentioned for Process 1.

This reaction is usually carried out in a conventional solvent which does not adversely influence the reaction such as dichloromethane, pyridine, N,N-dimethylformamide, 4-methyl-2-pentanone, tetrahydrofuran, etc., or a mixture thereof.

The reaction temperature is not critical and the reaction is usually carried out under from warming to heating.

(C) Method C :

The compound (II-b) or salts thereof can be prepared

by reducing the nitro group of the compound (X) or salts thereof.

Preferable salts of the compound (X) may be the same as those for the compound (II).

The method of reduction and the reaction conditions (e.g. reaction temperature, solvent, etc.) are substantially the same as those illustrated in Process 2, and therefore are to be referred to said explanation.

(D) Method D :

The compound (II-c) or salts thereof can be prepared by reacting the compound (II-b) or a reactive derivative at the amino group, or salts thereof with the compound (V) or a reactive derivative at the carboxy group, or salts thereof.

Suitable salts of the compound (I-c) can be referred to the ones as exemplified for the compound (II).

Suitable reactive derivative at the amino group of the compound (II-b) may be the same as those for the compound (I-a).

This reaction can be carried out in substantially the same manner as Process 3, and therefore the reaction mode and reaction condition [e.g. reactive derivatives, solvents reaction temperature, etc.] of this reaction are to be referred to those as explained in Process 3.

(E) Method E :

The compound (II-d) can be prepared by reacting the compound (VI) or its reactive derivative at the carboxy group, or salts thereof with the compound (VII).

This reaction is preferably carried out in the presence of a base and/or a condensing agent as illustrated in Process 3.

The reaction is usually carried out in a conventional solvent which does not adversely influence the reaction

such as water, acetone, dichloromethane, alcohol (e.g. methanol, ethanol, etc.), tetrahydrofuran, pyridine, N,N-dimethylformamide, etc., or a mixture thereof.

The reaction temperature is not critical and the reaction is usually carried out under from cooling to heating.

The object compound (I) stimulate presynaptic(neuronal) and/or postsynaptic (vascular) dopamine receptors that mediate inhibition of neurogenic release of catecholamine and/or dilatation of renal vasculature and remission of parkinsonism, respectively. Benzimidazole derivatives (I) effect on the cardiovascular system as a consequence of its interaction with dopaminergic and adrenergic receptors.

The object compound (I) and pharmaceutically acceptable salts thereof of the present invention are novel and display dopamine receptor stimulating effects; 5-HT receptor antagonism, especially 5-HT_2 receptor antagonism; α_1 receptor antagonism; and the like, and are useful as a dopamine receptor agonist; 5-HT receptor antagonist, especially 5-HT_2 receptor antagonist; α_1 receptor antagonist; and the like, for treating or preventing hypertension and other cardiovascular disorders (e.g. angina pectoris, congestive heart failure, myocardial infarction, etc.); Parkinsonism; hyperprolactinemia; disorders of peripheral perfusion such as Raynaud's phenomenon, Burger's diseases, and intermittent claudication; thrombotic and/or smooth muscle cell proliferative disease such as restenosis after percutaneous transluminal coronary angioplasty; hypercholesterolemia; urinary disturbance; and the like.

The compound (I) and pharmaceutically acceptable salts thereof may be also useful as a adrenolytic, tranquilizer, sedative, anti-emetic, hypothermic, skeletal muscle relaxant, anti-inflammatory, hypoglycemic, or anti-

viral agent.

Now in order to show the utility of the object compound (I) and pharmaceutically acceptable salts, the test data on dopamine receptor stimulating effects of the representative compound of the compound (I) of this invention are shown in the following.

Test Compound :

Compound A [The product of Example 3-2)]

Test [Dopamine receptor (DA_2 receptor) binding assay]

Test Method :

The affinity for DA_2 receptor of Test Compound was determined following in vitro receptor binding assays.

Male rats weighing 150-300 g were decapitated and the striatum were dissected from their brains. The tissue was homogenized in 40 volumes of buffer which consisted of 50 mM Tris-HCl (pH 7.5 at 25°C), 1 mM ethylenediaminetetraacetic acid, 5 mM potassium chloride, 2 mM calcium chloride, and 1 mM magnesium chloride. The homogenate was centrifuged at 50,000 g for 15 minutes. The pellet was resuspended in 80 volumes of the buffer. The tissue suspension was centrifuged and suspended again in the same way.

Incubation tubes received 100 µl of 2-(N-[2,3(n)-^{3}H]propyl-N-(2-aminofuranyl)-2'-ethylamino)-5-hydroxy-1,2,3,4-tetrahydronaphthalene, 10 µl of the Test Compound and 0.89 ml of tissue suspension during binding assays. The concentration of 2-(N-[2,3(n)-^{3}H]propyl-N-(2-aminofuranyl)-2'-ethylamino)-5-hydroxy-1,2,3,4-tetrahydronaphthalene was 1.5 nM. The final tissue concentration of rat striatum was 160 µg/ml. The tubes were incubated at 25°C for 45 minutes, and then filtered under vacuum through Whatman GF/B filters and washed three

times with 3 ml of ice-cold buffer. The filters were counted by liquid scintillation counter.

Specific binding of the 2-(N-[2,3(n)-^{3}H]propyl-N-(2-aminofuranyl)-2'-ethylamino)-5-hydroxy-1,2,3,4-tetrahydronaphthalene was determined in the presence of 1 μM apomorphine. The IC_{50} value of the Test Compound was calculated from the data of 2-(N-[2,3(n)-^{3}H]propyl-N-(2-aminofuranyl)-2'-ethylamino-5-hydroxy-1,2,3,4-tetrahydronaphthalene binding in the presence of 10^{-9}M, 10^{-8}M, 10^{-7}M, and 10^{-6}M Test compound.

Test Result :

Test Compound	IC_{50} (M)
Compound A	4.8×10^{-9}

For therapeutic administration, the object compound (I) and the pharmaceutically acceptable salts thereof of the present invention are used in the form of conventional pharmaceutical preparation which contains said compound, as an active ingredient, in admixture with pharmaceutically acceptable carriers such as an organic or inorganic solid or liquid excipient which is suitable for oral, parenteral and external administration.
The pharmaceutical preparations may be in solid form such as tablet, granule, powder, capsule, or liquid form such as solution, suspension, syrup, emulsion, lemonade, and the like.

If needed, there may be included in the above preparations auxiliary substances, stabilizing agents, wetting agents and other commonly used additives such as lactose, stearic acid, magnesium stearate, terra alba,

sucrose, corn starch, talc, gelatin, agar, pectin, peanut oil, olive oil, cacao butter, ethylene glycol, tartaric acid, citric acid, fumaric acid, and the like.

While the dosage of the compound (I) may vary from and also depend upon the age, conditions of the patient, a kind of diseases, a kind of the compound (I) to be applied, etc. In general, amount between about 0.001 mg and about 300 mg, preferably about 0.1 mg to about 50 mg per day may be administered to a patient. An average single dose of about 0.001 mg, 0.01 mg, 0.03 mg, 0.1 mg, 0.3 mg, 0.6 mg, 1.0 mg, 3.0 mg, 10.0 mg, 50.0 mg, 100.0 mg, of the object compound (I) of the present invention may be used as adrenolytic, hypotensive, cardiovascular, tranquilizer, sedative, anti-emetic, hypothermic, skeletal muscle relaxant, anti-inflammatory, and anti-viral agents.

The following Preparations and Examples are given for the purpose of illustrating this invention in more detail.

- to be continued on the next page -

Preparation 1-1)

Acetic formic anhydride, which was prepared from acetic anhydride (24 ml) and formic acid (12 ml), was added to a solution of ethyl 4-amino-3-methylbenzoate (21.7 g) in dichloromethane (200 ml) at 20°C. After stirring at 20°C for 30 minutes, the mixture was concentrated in vacuo. The residue was poured into a mixture of ethyl acetate and water. The organic layer was separated, washed with aqueous sodium bicarbonate and brine, and dried over magnesium sulfate. After evaporation of the solvent, the crystalline residue was recrystallized from a mixture of ethyl acetate and hexane to give ethyl 4-formamido-3-methylbenzoate (22.0 g) as colorless crystals.

NMR (CD_3OD, δ) : 1.38 (3H, t, J=7Hz), 2.33 (3H, s), 4.34 (2H, q, J=7Hz), 7.31 (0.2H, d, J=8Hz), 7.79 (0.2H, d, J=1Hz), 7.82-7.91 (1.8H, m), 8.04 (0.8H, d, J=8Hz), 8.37 (0.8H, s), 8.62 (0.2H, s)

Preparation 1-2)

Ethyl 4-formamido-3-methylbenzoate (2.0 g) was added to a mixture of 70% nitric acid (5 ml) and conc. sulfuric acid (5 ml) at 10°C. After stirring at 10°C for 2 hours, the mixture was poured into a stirring ice-water. The precipitates were filtered, washed with water, and then dissolved in chloroform. The solution was dried over magnesium sulfate and evaporated. The crystalline residue was recrystallized from a mixture of chloroform and hexane to give ethyl 4-formamido-3-methyl-5-nitrobenzoate (2.06 g).

NMR ($CDCl_3$, δ) : 1.42 (3H, t, J=7Hz), 2.43 (3H, br s), 4.44 (2H, q, J=7Hz), 8.20 (1H, d, J=2Hz), 8.41 (1H, d, J=2Hz), 8.53 (1H, d, J=2Hz), 8.68 (1H, br s)

Preparation 1-3)

A mixture of ethyl 4-formamido-3-methyl-5-nitrobenzoate (2.04 g), 1-bromo-4-chlorobutane (1.40 ml) and potassium carbonate (3.35 g) in dimethylformamide (20 ml) was heated at 50°C for 30 minutes, and then partitioned between ethyl acetate and water. The organic layer was separated, washed with water and brine, and dried over magnesium sulfate. After evaporation of the solvent, the oily residue was purified by column chromatography eluting with a mixture of ethyl acetate and hexane (1:10 - 1:2) to give ethyl 4-[N-(4-chlorobutyl)formamido]-3-methyl-5-nitrobenzoate (2.31 g) as a yellow oil.

NMR ($CDCl_3$, δ) : 1.42 (1H, t, J=7Hz), 1.43 (2H, t, J=7Hz), 1.52-1.85 (4H, m), 2.40 (1H, s), 2.42 (2H, s), 3.40-3.80 (4H, m), 4.45 (0.7H, q, J=7Hz), 4.46 (1.3H, q, J=7Hz), 8.14 (0.3H, s), 8.19-8.28 (1H, m), 8.33-8.40 (1H, m), 8.45 (0.7H, d, J=2Hz)

Preparation 1-4)

To a mixture of ethyl 4-[N-(4-chlorobutyl)formamido]-3-methyl-5-nitrobenzoate (11.1 g) in a mixture of acetic acid (40 ml) and ethanol (40 ml) was added iron powder (9.0 g) and the mixture was refluxed for 3 hours. The reaction mixture was filtered, and the filtrate was partitioned between ethyl acetate and water. The organic layer was separated, washed with aqueous sodium bicarbonate and brine, and dried over magnesium sulfate. After evaporation of the solvent, the crystalline residue was recrystallized from a mixture of ethyl acetate and hexane to give ethyl 1-(4-chlorobutyl)-7-methyl-5-benzimidazolecarboxylate (7.37 g) as pale yellow crystals.

NMR ($CDCl_3$, δ) : 1.41 (3H, t, J=6Hz), 1.75-1.93 (2H, m), 1.93-2.14 (2H, m), 2.72 (3H, s), 3.56 (2H,

t, J=6Hz), 4.31-4.50 (4H, m), 7.76 (1H, s), 7.89 (1H, s), 8.36 (1H, s)

Preparation 1-5)

To a solution of ethyl 1-(4-chlorobutyl)-7-methyl-5-benzimidazolecarboxylate (7.0 g) in tetrahydrofuran (70 ml) were added 1N aqueous sodium hydroxide (35 ml) and methanol (35 ml), and the mixture was stirred at 25°C overnight. After evaporation of the organic solvent, the residue was neutralized with 1N hydrochloric acid (35 ml). The precipitates were filtered and recrystallized from ethanol to give 1-(4-chlorobutyl)-7-methyl-5-benzimidazole carboxylic acid (5.24 g) as pale yellow crystals.

NMR (DMSO-d_6, δ) : 1.66-2.00 (4H, m), 2.72 (3H, s), 3.70 (2H, t, J=6Hz), 4.45 (2H, t, J=6Hz), 7.63 (1H, s), 8.06 (1H, s), 8.32 (1H, s)

Preparation 1-6)

To a mixture of 1-(4-chlorobutyl)-7-methyl-5-benzimidazole-5-carboxylic acid (1.0 g) and diphenylphosphoryl azide (1.24 g) in tert-butyl alcohol (20 ml) was added triethylamine (0.627 ml) at 20°C. After refluxing overnight, the mixture was partitioned between ethyl acetate and aqueous sodium bicarbonate. The organic layer was separated, washed with water and brine, and dried over magnesium sulfate. After evaporation of the solvent, the residue was purified by column chromatography on silica gel eluting with 5% methanol in chloroform. The fractions containing the desired compound were collected and evaporated. Recrystallization from a mixture of ethyl acetate and hexane gave 1-(4-chlorobutyl)-5-(t-butoxycarbonylamino)-7-methylbenzimidazole (0.98 g) as colorless crystals.

NMR ($CDCl_3$, δ) : 1.53 (9H, s), 2.67 (3H, s), 3.55 (2H, t, J=6Hz), 4.35 (2H, t, J=7Hz), 6.49 (1H,

br s), 7.27 (1H, br s), 7.45 (1H, d, J=2Hz), 7.78 (1H, s)

Preparation 2

A mixture of 5-nitrobenzimidazole (25.0 g), 1-bromo-4-chlorobutane (26 ml) and potassium carbonate (106 g) in dimethylformamide (300 ml) was stirred at 20°C for 2 hours. The mixture was filtered, concentrated and then poured into a mixture of ethyl acetate and aqueous sodium bicarbonate. The organic layer was separated, washed with water and brine, dried over magnesium sulfate and evaporated. The residue was purified by column chromatography on silica gel (600 g) eluting with 10% methanol in chloroform. Twice recrystallizations from ethyl acetate yielded 1-(4-chlorobutyl)-5-nitrobenzimidazole (14.8 g) as pale yellow crystals.

NMR ($CDCl_3$, δ) : 1.75-1.93 (2H, m), 2.03-2.22 (2H, m), 3.60 (2H, t, J=6Hz), 4.30 (2H, t, J=7Hz), 7.49 (1H, d, J=10Hz), 8.09 (1H, s), 8.28 (1H, dd, J=10Hz, 2Hz), 8.74 (1H, d, J=2Hz)

Preparation 3

To a solution of 1-(4-chlorobutyl)-5-nitrobenzimidazole (200 mg) in methanol (30 ml) were added 0.65N hydrogen chloride in methanol (3.0 ml) and 10% palladium on activated carbon (84 mg). The mixture was shaken at 20°C under hydrogen for 1 hour, and then filtered and concentrated to give 5-amino-1-(4-chlorobutyl)benzimidazole dihydrochloride (261.3 mg) as a brown oil.

NMR (CD_3OD, δ) : 1.81-2.01 (2H, m), 2.09-2.30 (2H, m), 3.66 (2H, t, J=6Hz), 4.67 (2H, t, J=6Hz), 7.73 (1H, dd, J=10Hz, 2Hz), 8.05 (1H, d, J=2Hz), 8.25 (1H, d, J=10Hz), 9.71 (1H, s)

Preparation 4-1)

To a suspension of 5-amino-1-(4-chlorobutyl)benzimidazole dihydrochloride (100 mg) in dichloromethane (2 ml) was added 2,6-lutidine (109 mg) at 20°C, followed by acetyl chloride (32 mg) at 0°C. After stirring at 20°C for 30 minutes, the reaction mixture was poured into a mixture of ethyl acetate and aqueous sodium bicarbonate. The organic layer was separated, washed with water and brine, and dried over magnesium sulfate. After evaporation of the solvent, the residue was purified by column chromatography on silica gel (25 g) eluting with 6% methanol in chloroform to give 5-acetamido-1-(4-chlorobutyl)benzimidazole (55 mg) as a brown solid.

NMR ($CDCl_3$, δ) : 1.68-1.87 (2H, m), 1.95-2.16 (2H, m), 2.20 (3H, s), 3.55 (2H, t, J=6Hz), 4.21 (2H, t, J=6Hz), 7.33 (1H, d, J=9Hz), 7.49 (1H, br s), 7.58 (1H, dd, J=9Hz, 2Hz), 7.80 (1H, d, J=2Hz), 7.89 (1H, s)

The following compounds were obtained in substantially the same manner as that of Preparation 4-1).

Preparation 4-2)

1-(4-Chlorobutyl)-5-propionamidobenzimidazole

NMR ($CDCl_3$, δ) : 1.27 (3H, t, J=7Hz), 1.70-1.88 (2H, m), 1.98-2.06 (2H, m), 2.44 (2H, q, J=7Hz), 3.54 (2H, t, J=7Hz), 4.20 (2H, t, J=7Hz), 7.32 (1H, d, J=10Hz), 7.62 (1H, dd, J=10Hz, 2Hz), 7.66 (1H, br s), 7.81 (1H, d, J=2Hz), 7.87 (1H, s)

Preparation 4-3)

5-Butyramido-1-(4-chlorobutyl)benzimidazole

NMR ($CDCl_3$, δ) : 1.03 (3H, t, J=6Hz), 1.71-1.91 (4H, m), 1.98-2.16 (2H, m), 2.38 (2H, t, J=6Hz), 3.54 (2H, t, J=6Hz), 4.22 (2H, t, J=6Hz), 7.35 (1H,

d, J=8Hz), 7.62 (1H, dd, J=8Hz, 2Hz), 7.79 (1H, d, J=2Hz), 7.88 (1H, s)

Preparation 4-4)

1-(4-Chlorobutyl)-5-(2-methylpropionamido)-benzimidazole

NMR ($CDCl_3$, δ) : 1.30 (6H, d, J=6Hz), 1.69-1.91 (2H, m), 1.96-2.18 (2H, m), 2.46-2.66 (1H, m), 3.56 (2H, t, J=5Hz), 4.22 (2H, t, J=5Hz), 7.36 (1H, d, J=8Hz), 7.67 (1H, d, J=7Hz), 7.81 (1H, s), 7.90 (1H, s)

Preparation 5

A mixture of 4-nitrobenzimidazole (5.27 g), 1-bromo-4-chlorobutane (5.6 ml) and potassium carbonate (22.3 g) in dimethylformamide (50 ml) was stirred at 20°C for 2 hours. The reaction mixture was poured into a mixture of ethyl acetate and aqueous sodium bicarbonate. The organic layer was separated, washed with water and brine, and dried over magnesium sulfate. Concentration and chromatography on silica gel (200 g) eluting with chloroform followed by 5% methanol in chloroform gave 1-(4-chlorobutyl)-7-nitrobenzimidazole (2.77 g) as a brown solid.

NMR ($CDCl_3$, δ) : 1.68-2.00 (4H, m), 3.52 (2H, t, J=7Hz), 4.51 (2H, t, J=7Hz), 7.38 (1H, t, J=9Hz), 7.96-8.16 (3H, m)

Elution with 5% methanol in chloroform was continued to give 1-(4-chlorobutyl)-4-nitrobenzimidazole (4.77 g) as a brown solid.

NMR ($CDCl_3$, δ) : 1.78-1.94 (2H, m), 2.04-2.42 (2H, m), 3.58 (2H, t, J=7Hz), 4.35 (2H, t, J=7Hz), 7.44 (1H, t, J=9Hz), 7.76 (1H, dd, J=9Hz, 2Hz), 8.17-8.22 (2H, m)

Preparation 6

10% Palladium on activated carbon (0.45 g) was added to a solution of 1-(4-chlorobutyl)-4-nitrobenzimidazole (1.49 g) in methanol (50 ml). The mixture was shaken at 20°C under hydrogen for 1 hour, and then filtered and concentrated to give 4-amino-1-(4-chlorobutyl)-benzimidazole dihydrochloride (1.81 g) as a brown oil.

NMR (CD_3OD, δ) : 1.80-1.97 (2H, m), 2.07-2.26 (2H, m), 3.66 (2H, t, J=6Hz), 4.58 (2H, t, J=7Hz), 7.26 (1H, dd, J=7Hz, 2Hz), 7.51-7.62 (2H, m), 9.54 (1H, s)

Preparation 7-1)

To a suspension of 4-amino-1-(4-chlorobutyl)-benzimidazole dihydrochloride (500 mg) in dichloromethane (15 ml) was added 2,6-lutidine (542 mg) at 20°C, followed by acetyl chloride (0.14 ml) at 0°C. After stirring at 20°C for 1 hour, the reaction mixture was poured into a mixture of ethyl acetate and aqueous sodium bicarbonate. The organic layer was separated, washed with water and brine, and dried over magnesium sulfate. After evaporation of the solvent, the residue was purified by column chromatography on silica gel (50 g) eluting with 2% methanol in chloroform to give 4-acetamido-1-(4-chlorobutyl)benzimidazole (399 mg) as a brown solid.

NMR ($CDCl_3$, δ) : 1.71-1.89 (2H, m), 2.00-2.17 (2H, m), 2.28 (3H, s), 3.55 (2H, t, J=7Hz), 4.22 (2H, t, J=7Hz), 7.12 (1H, dd, J=8Hz, 1Hz), 7.29 (1H, t, J=8Hz), 7.81 (1H, s), 8.24 (1H, d, J=8Hz), 8.45 (1H, br s)

Preparation 7-2)

1-(4-Chlorobutyl)-4-propionamidobenzimidazole was obtained in substantially the same manner as that of Preparation 7-1).

NMR ($CDCl_3$, δ) : 1.30 (3H, t, J=7Hz), 1.71-1.88 (2H, m), 1.99-2.15 (2H, m), 2.53 (2H, q, J=7Hz), 3.55 (2H, t, J=6Hz), 4.23 (2H, t, J=7Hz), 7.12 (1H, dd, J=9Hz, 2Hz), 7.30 (1H, t, J=8Hz), 7.81 (1H, s), 8.28 (1H, d, J=9Hz), 8.42 (1H, br s)

Preparation 8-1)

To a suspension of 1-(4-chlorobutyl)-7-methylbenzimidazole-5-carboxylic acid (500 mg) in 1,4-dioxane (5 ml) were added diphenylphosphoryl azide (0.48 ml) and triethylamine (0.31 ml) at 20°C. The reaction mixture was heated at 80°C under stirring for 3 hours, and then morpholine (0.20 ml) was added. After stirring for 1 hour at 80°C, the reaction mixture was poured into a mixture of ethyl acetate and aqueous sodium bicarbonate. The organic layer was separated, washed with water and brine, and dried over magnesium sulfate. After evaporation of the solvent, the residue was purified by column chromatography on silica gel (50 g) eluting with 5% methanol in chloroform to yield 1-(4-chlorobutyl)-7-methyl-5-(4-morpholinylcarboxamido)benzimidazole (646 mg) as a brown oil.

NMR ($CDCl_3$, δ) : 1.70-1.89 (2H, m), 1.89-2.07 (2H, m), 2.62 (3H, s), 3.41-3.60 (6H, m), 3.65-3.75 (4H, m), 4.33 (2H, t, J=7Hz), 6.78 (1H, br s), 7.19 (1H, d, J=2Hz), 7.42 (1H, d, J=2Hz), 7.75 (1H, s)

Preparation 8-2)

1-(4-Chlorobutyl)-7-methyl-5-(3,3-dimethylureido)benzimidazole was obtained in substantially the same manner as that of Preparation 8-1).

NMR ($CDCl_3$, δ) : 1.71-1.90 (2H, m), 1.90-2.08 (2H, m), 2.64 (3H, s), 3.04 (6H, s), 3.54 (2H, t, J=6Hz), 4.33 (2H, t, J=6Hz), 6.42 (1H, br s), 7.25 (1H, d, J=2Hz), 7.43 (1H, d, J=2Hz),

7.77 (1H, s)

Preparation 9-1)

Ethyl 2-amino-3-nitrobenzoate (10 g) was added to acetic formic anhydride, which was prepared with acetic anhydride (40 ml) and formic acid (20 ml) at 20°C. The reaction mixture was heated at 50°C for 3.5 hours, and then partitioned between ethyl acetate and aqueous sodium bicarbonate. The organic layer was separated, washed with water and brine, and dried over magnesium sulfate. After evaporation of the solvent, the oily residue was crystallized from isopropyl ether and the crystals were filtered to give ethyl 2-formamido-3-nitrobenzoate (4.56 g). The mother liquid was purified by column chromatography on silica gel eluting with chloroform to give other crystals of ethyl 2-formamido-3-nitrobenzoate (4.73 g).

NMR ($CDCl_3$, δ) : 1.44 (3H, t, J=7Hz), 4.44 (2H, q, J=7Hz), 7.38 (1H, t, J=7Hz), 8.12 (1H, d, J=7Hz), 8.26 (1H, d, J=7Hz), 8.48 (1H, s)

Preparation 9-2)

To a solution of ethyl 2-formamido-3-nitrobenzoate (3.26 g) in ethanol (30 ml) were added iron powder (3.82 g) and acetic acid (15 ml) at 20°C. After being stirred at 90°C for 3 houts, the reaction mixture was filtered through cellulose powder and partitioned between ethyl acetate and aqueous sodium bicarbonate. The organic layer was separated, washed with water and brine, and dried over magnesium sulfate. Evaporation of the solvent gave ethyl 4-benzimidazolecarboxylate (1.50 g) as a pale yellow solid.

NMR ($CDCl_3$, δ) : 1.47 (3H, t, J=7Hz), 4.49 (2H, q, J=7Hz), 7.35 (1H, t, J=8Hz), 7.98 (1H, d, J=8Hz), 8.07 (1H, d, J=8Hz), 8.18 (1H, s)

Preparation 9-3)

To a solution of ethyl 4-benzimidazolecarboxylate (1.09 g) in N,N-dimethylformamide (30 ml) were added 1-bromo-4-chrolobutane (1.47 g) and potassium carbonate (3.96 g). The reaction mixture was heated at 50°C for 1.5 hours, and then partitioned between ethyl acetate and aqueous sodium bicarbonate. The organic layer was separatd, washed with water and brine, and dried over magnesium sulfate. Evaporation of the solvent gave a mixture of two isomers, which was separated by column chromatography on silica gel eluting with a mixture of ethyl acetate and hexane (1:1 to 1:0, V/V) to give ethyl 1-(4-chlorobutyl)-4-benzimidazolecarboxylate (1.00 g, polar) (Compound A) and ethyl 1-(4-chlorobutyl)-7-benzimidazolecarboxylate (0.75 g) (Compound B).

Compound A :

Rf : 0.2 (silica gel, ethyl acetate)

NMR ($CDCl_3$, δ) : 1.48 (3H, t, J=7Hz), 1.71-1.88 (2H, m), 2.00-2.20 (2H, m), 3.55 (2H, t, J=6Hz), 4.28 (2H, t, J=7Hz), 4.53 (2H, q, J=7Hz), 7.37 (1H, t, J=8Hz), 7.60 (1H, d, J=8Hz), 8.00 (1H, d, J=8Hz), 8.09 (1H, s)

Compound B :

Rf : 0.4 (silica gel, ethyl acetate)

NMR ($CDCl_3$, δ) : 1.45 (3H, t, J=8Hz), 1.66-1.98 (4H, m), 3.52 (2H, t, J=7Hz), 4.45 (2H, q, J=7Hz), 4.61 (2H, t, J=7Hz), 7.32 (1H, t, J=7Hz), 7.90 (1H, d, J=7Hz), 7.93 (1H, s), 8.00 (1H, d, J=7Hz)

Preparation 9-4)

To a solution of ethyl 1-(4-chlorobutyl)-4-benzimidazolecarboxylate (900 mg) were added 1N aqueous

sodium hydroxide (4 ml) and methanol, and the reaction mixture was stirred at 20°C overnight. The mixture was neutralized with 1N hydrochloric acid (4 ml) and partitioned between ethyl acetate and water. The organic layer was separated, washed with brine, and dried over magnesium sulfate. After the evaporation of solvent, the crude crystals were recrystallized from ethanol to give 1-(4-chlorobutyl)-4-benzimidazolecarboxylic acid (379 mg). The second crystals (100 mg) were obtained from mother liquid.

NMR (CD_3OD, δ) : 1.72-1.90 (2H, m), 2.00-2.19 (2H, m), 3.61 (2H, t, J=5Hz), 4.44 (2H, t, J=5Hz), 7.49 (1H, t, J=7Hz), 7.91 (1H, d, J=7Hz), 7.99 (1H, d, J=7Hz), 8.54 (1H, s)

Preparation 9-5)

A mixture of 1-(4-chlorobutyl)-4-benzimidazole-carboxylic acid (500 mg), 1-hydroxybenzotriazole (294 mg) and 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (417 mg) in N,N-dimethylformamide (8 ml) was stirred at 20°C for 1 hour, and then morpholine (207 mg) was added thereto. After stirring at 20°C for 1 hour, the raction mixture was partitioned between ethyl acetate and aqueous sodium bicarbonate. The organic layer was separated, washed with water and brine, and dried over magnesium sulfate. After the evaporation of solvent, the residue was purified by column chromatography on silica gel eluting with 5% methanol in chloroform to give 1-(4-chlorobutyl)-4-(morpholinocarbonyl)benzimidazole (398 mg) as an oil.

NMR ($CDCl_3$, δ) : 1.73-1.90 (2H, m), 2.00-2.15 (2H, m), 3.36 (2H, br t), 3.56 (2H, t, J=6Hz), 3.65 (2H, br t), 3.80-3.88 (2H, m), 3.88-3.98 (2H, m), 4.24 (2H, t, J=6Hz), 7.31-7.51 (3H, m), 7.95 (1H, s)

Preparation 10

1-(4-Chlorobutyl)-4-(pyrrolidin-1-ylcarbonyl)-benzimidazole was obtained in substantially the same manner as that of Preparation 9-5).

NMR ($CDCl_3$, δ) : 1.73-2.17 (8H, m), 3.38 (2H, t, J=7Hz), 3.56 (2H, t, J=7Hz), 3.78 (2H, t, J=7Hz), 4.25 (2H, t, J=7Hz), 7.27-7.49 (3H, m), 7.94 (1H, s)

Preparation 11

1-(4-Chlorobutyl)-4-(4-methylpiperazin-1-yl)-carbonylbenzimidazole was obtained in substantially the same manner as that of Preparation 9-5).

NMR ($CDCl_3$, δ) : 1.71-1.91 (2H, m), 2.00-2.18 (2H, m), 2.32 (3H, s), 2.36 (2H, br t, J=5Hz), 2.57 (2H, br t, J=5Hz), 3.38 (2H, br t, J=5Hz), 3.57 (2H, t, J=5Hz), 3.95 (2H, br t, J=5Hz), 4.25 (2H, t, J=5Hz), 7.30-7.50 (3H, m), 7.93 (1H, s)

Preparation 12

1-(4-Chlorobutyl)-4-(N,N-dimethylcarbamoyl)-benzimidazole was obtained in substantially the same manner as that of Preparation 9-5).

NMR ($CDCl_3$, δ) : 1.71-1.90 (2H, m), 1.97-2.17 (2H, m), 2.95 (3H, s), 3.21 (3H, s), 3.58 (2H, t, J=7Hz), 4.25 (2H, t, J=7Hz), 7.30-7.49 (3H, m), 7.92 (1H, s)

Preparation 13

A solution of 1-(4-chlorobutyl)-4-benzimidazolecarboxylic acid (300 mg) in 2-propanol (10 ml) containing sulfuric acid (0.5 ml) was heated to reflux for 24 hours. The reaction mixture was poured into a mixture of ethyl acetate and aqueous sodium bicarbonate. The organic layer was separated, washed with water and

brine, and dried over magnesium sulfate. After the evaporation of solvent, isopropyl 1-(4-chlorobutyl)-4-benzimidazolecarboxylate (217 mg) was obtained as an yellow oil.

NMR ($CDCl_3$, δ) : 1.45 (6H, d, J=7Hz), 1.70-1.89 (2H, m), 2.00-2.17 (2H, m), 3.55 (2H, t, J=6Hz), 4.28 (2H, t, J=6Hz), 5.30-5.45 (1H, m), 7.36 (1H, t, J=9Hz), 7.59 (1H, d, J=9Hz), 7.94 (1H, d, J=9Hz), 8.05 (1H, s)

Preparation 14

To a solution of 1-(4-chlorobutyl)-4-benzimidazole-carboxylic acid (1.0 g) in dichloromethane (20 ml) were added oxalyl chloride (0.69 ml) and dimethylformamide (1 drop) at 20°C. The mixture was stirred at 20°C for 2 hours, and then evaporated to give 1-(4-chlorobutyl)-4-benzimidazolecarbonyl chloride hydrochloride (1.30 g) as colorless crystals.

NMR ($CDCl_3$, δ) : 1.95-2.08 (2H, m), 2.24-2.34 (2H, m), 3.66 (2H, t, J=7Hz), 4.98 (2H, t, J=7Hz), 7.80 (1H, t, J=8Hz), 8.15 (1H, d, J=8Hz), 8.42 (1H, d, J=8Hz)

Preparation 15

1-(4-Chlorobutyl)-4-benzimidazolecarbonyl chloride hydrochloride (200 mg) was added to a mixture of aniline (91 mg) and 4-(dimethylamino)pyridine (252 mg) in dichloromethane (8 ml) at 20°C. The mixture was stirred at 20°C for 30 minutes, and then evaporated. The residue was purified by column chromatography on silica gel eluting with chloroform to give 1-(4-chlorobutyl)-4-(phenylcarbamoyl)benzimidazole (169 mg) as colorless crystals.

NMR ($CDCl_3$, δ) : 1.76-1.90 (2H, m), 2.04-2.18 (2H, m), 3.57 (2H, t, J=7Hz), 4.30 (2H, t, J=7Hz),

7.13 (1H, t, J=7Hz), 7.38 (2H, t, J=7Hz), 7.46 (1H, t, J=8Hz), 7.58 (1H, dd, J=1, 8Hz), 7.88 (2H, d, J=7Hz), 8.02 (1H, s), 8.26 (1H, dd, J=1, 8Hz)

The following compounds were obtained in substantially the same manner as that of Preparation 15.

Preparation 16

1-(4-Chlorobutyl)-4-(pyrazin-2-ylcarbamoyl)-benzimidazole

NMR ($CDCl_3$, δ) : 1.80-1.93 (2H, m), 2.10-2.22 (2H, m), 3.58 (2H, t, J=7Hz), 4.34 (2H, t, J=7Hz), 7.50 (1H, t, J=8Hz), 7.67 (1H, d, J=8Hz), 8.10 (1H, s), 8.30 (2H, d, J=8Hz), 8.37 (2H, s)

Preparation 17

1-(4-Chlorobutyl)-4-(pyrimidin-2-ylcarbamoyl)-benzimidazole

NMR ($CDCl_3$, δ) : 1.78-1.90 (2H, m), 2.08-2.18 (2H, m), 3.57 (2H, t, J=7Hz), 4.32 (2H, t, J=7Hz), 7.04 (1H, t, J=5Hz), 7.48 (1H, t, J=8Hz), 7.63 (1H, dd, J=1, 8Hz), 8.10 (1H, s), 8.34 (1H, dd, J=1, 8Hz), 8.74 (2H, d, J=5Hz)

Preparation 18

1-(4-Chlorobutyl)-4-(pyrimidin-4-ylcarbamoyl)-benzimidazole

NMR ($CDCl_3$, δ) : 1.80-1.92 (2H, m), 2.08-2.20 (2H, m), 3.58 (2H, t, J=7Hz), 4.34 (2H, t, J=7Hz), 7.50 (1H, t, J=8Hz), 7.68 (1H, d, J=8Hz), 8.12 (1H, s), 8.26 (1H, d, J=8Hz), 8.46 (1H, d, J=6Hz), 8.68 (1H, d, J=6Hz), 9.00 (1H, s)

Preparation 19

1-(4-Chlorobutyl)-4-(thiazol-2-ylcarbamoyl)-benzimidazole

NMR ($CDCl_3$, δ) : 1.80-1.92 (2H, m), 2.10-2.20 (2H, m), 3.56 (2H, t, J=7Hz), 4.33 (2H, t, J=7Hz), 7.03 (1H, d, J=4Hz), 7.50 (1H, t, J=8Hz), 7.56 (1H, d, J=4Hz), 7.66 (1H, d, J=8Hz), 8.06 (1H, s), 8.27 (2H, d, J=8Hz)

Preparation 20

1-(4-Chlorobutyl)-4-[(1,3,4-thiadiazol-2-yl)carbamoyl]benzimidazole

NMR ($CDCl_3$, δ) : 1.81-1.94 (2H, m), 2.10-2.22 (2H, m), 3.61 (2H, t, J=7Hz), 4.36 (2H, t, J=7Hz), 7.52 (1H, t, J=8Hz), 7.72 (1H, dd, J=1, 8Hz), 8.18 (1H, s), 8.25 (1H, dd, J=1, 8Hz), 8.91 (1H, s)

Preparation 21

1-(4-Chlorobutyl)-4-[(2-thiazolin-2-yl)carbamoyl]-benzimidazole

NMR ($CDCl_3$, δ) : 1.78-1.88 (2H, m), 2.07-2.18 (2H, m), 3.35 (2H, t, J=9Hz), 3.56 (2H, t, J=7Hz), 4.09 (2H, t, J=9Hz), 4.30 (2H, t, J=7Hz), 7.45 (1H, t, J=8Hz), 7.63 (1H, dd, J=1, 8Hz), 8.00 (1H, s), 8.20 (1H, dd, J=1, 8Hz)

The following compounds were obtained in substantially the same manner as that of Preparation 9-5).

Preparation 22

1-(4-Chlorobutyl)-4-(cyclopropylcarbamoyl)-benzimidazole

NMR ($CDCl_3$, δ) : 0.68-0.75 (2H, m), 0.82-0.95 (2H, m), 1.75-1.88 (2H, m), 2.02-2.16 (2H, m),

3.02-3.12 (1H, m), 3.55 (2H, t, J=7Hz), 4.26 (2H, t, J=7Hz), 7.40 (1H, t, J=8Hz), 7.52 (1H, d, J=8Hz), 7.92 (1H, s), 8.20 (1H, d, J=8Hz)

Preparation 23

1-(4-Chlorobutyl)-4-(furfurylcarbamoyl)benzimidazole

NMR ($CDCl_3$, δ) : 1.74-1.86 (2H, m), 2.02-2.16 (2H, m), 3.54 (2H, t, J=7Hz), 4.27 (2H, t, J=7Hz), 4.77 (2H, d, J=7Hz), 6.33 (2H, s), 7.38 (1H, s), 7.42 (1H, t, J=8Hz), 7.55 (1H, d, J=8Hz), 7.95 (1H, s), 8.22 (1H, d, J=8Hz)

Preparation 24

1-(4-Chlorobutyl)-4-(morpholinocarbamoyl)-benzimidazole

NMR ($CDCl_3$, δ) : 1.77-1.88 (2H, m), 2.05-2.16 (2H, m), 3.10 (4H, t, J=5Hz), 3.56 (2H, t, J=7Hz), 3.90 (4H, t, J=5Hz), 4.29 (2H, t, J=7Hz), 7.43 (1H, t, J=8Hz), 7.56 (1H, d, J=8Hz), 7.97 (1H, s), 8.22 (1H, d, J=8Hz)

Example 1

A mixture of 1-(4-chlorobutyl)-5-(t-butoxycarbonylamino)-7-methylbenzimidazole (1.0 g), 4-phenyl-1,2,3,6-tetrahydropyridine hydrochloride (694 mg), sodium iodide (666 mg) and potassium carbonate (1.23 g) in dimethylformamide (20 ml) was heated at 80°C for 4 hours, and then the reaction mixture was partitioned between ethyl acetate and water. The organic layer was separated, washed with water and brine, and dried over magnesium sulfate. After evaporation of the solvent, the residue was purified by column chromatography eluting with 5% methanol in chloroform, and recrystallized from a mixture of ethyl acetate and hexane to give 5-(t-butoxycarbonylamino)-7-methyl-1-[4-(4-phenyl-1,2,3,6-

tetrahydro-1-pyridyl)butyl]benzimidazole (0.95 g) as colorless crystals.

NMR ($CDCl_3$, δ) : 1.53 (9H, s), 1.57-1.73 (2H, m), 1.81-2.01 (2H, m), 2.42-2.62 (2H, m), 2.62-2.73 (5H, m), 3.08-3.17 (2H, m), 4.34 (2H, t, J=7Hz), 6.01-6.09 (1H, m), 6.49 (1H, br s), 7.19-7.47 (7H, m), 7.79 (1H, s)

Example 2

To a solution of 5-(t-butoxycarbonylamino)-7-methyl-1-[4-(4-phenyl-1,2,3,6-tetrahydro-1-pyridyl)butyl]-benzimidazole (0.90 g) in 1,4-dioxane (10 ml) was added 1N hydrogen chloride in methanol (10.5 ml), and the mixture was heated at 50°C for 2 hours. The precipitates were filtered and washed with 1,4-dioxane to give 5-amino-7-methyl-1-[4-(4-phenyl-1,2,3,6-tetrahydro-1-pyridyl)butyl]-benzimidazole trihydrochloride (0.76 g) as pale yellow crystals.

mp : 180-185°C (dec.)

NMR (CD_3OD, δ) : 1.92-2.24 (4H, m), 2.75-3.11 (2H, m), 2.89 (3H, s), 3.83-3.47 (2H, m), 3.73-3.94 (2H, m), 4.04-4.23 (1H, m), 4.78 (2H, t, J=7Hz), 6.13 (1H, br s), 7.24-7.52 (6H, m), 7.72 (1H, d, J=2Hz), 9.63 (1H, s)

Example 3-1)

To a solution of 5-amino-7-methyl-1-[4-(4-phenyl-1,2,3,6-tetrahydro-1-pyridyl)butyl]benzimidazole trihydrochloride (250 mg) in dimethylformamide (5 ml) was added 2,6-lutidine (0.31 ml) at 20°C, followed by acetyl chloride (50 mg). The mixture was stirred at 20°C for 2 hours, and then partitioned between ethyl acetate and hexane. The organic layer was separated, washed with water and brine, and dried over magnesium, sulfate. After evaporation of the solvent, the residue was purified by

column chromatography on silica gel eluting with 5% methanol in chloroform, and recrystallized from a mixture of chloroform and hexane to give 5-acetamido-7-methyl-1-[4-(4-phenyl-1,2,3,6-tetrahydro-1-pyridyl)butyl]-benzimidazole (125 mg) as colorless crystals.

NMR ($CDCl_3$, δ) : 1.52-1.78 (2H, m), 1.81-2.03 (2H, m), 2.18 (3H, s), 2.48 (2H, t, J=7Hz), 2.50-2.61 (2H, m), 2.68 (3H, s), 2.61-2.74 (2H, m), 3.04-3.18 (2H, m), 4.33 (2H, t, J=7Hz), 6.00-6.08 (1H, m), 7.15-7.43 (6H, m), 7.59 (1H, d, J=2Hz), 7.81 (1H, s)

The following compounds were obtained in substantially the same manner as that of Example 3-1).

Example 3-2)

7-Methyl-1-[4-(4-phenyl-1,2,3,6-tetrahydro-1-pyridyl)butyl]-5-propionamidobenzimidazole

NMR ($CDCl_3$, δ) : 1.27 (3H, t, J=7Hz), 1.52-1.78 (2H, m), 1.81-2.03 (2H, m), 2.40 (2H, q, J=7Hz), 2.48 (2H, t, J=7Hz), 2.50-2.61 (2H, m), 2.68 (3H, s), 2.61-2.74 (2H, m), 3.64-3.18 (2H, m), 4.33 (2H, t, J=7Hz), 6.00-6.08 (1H, m), 7.15-7.43 (6H, m), 7.59 (1H, d, J=2Hz), 7.81 (1H, s)

Example 3-3)

5-Butyramido-7-methyl-1-[4-(4-phenyl-1,2,3,6-tetrahydro-1-pyridyl)butyl]benzimidazole

NMR ($CDCl_3$, δ) : 1.03 (2H, t, J=7Hz), 1.5-2.1 (6H, m), 2.37 (2H, t, J=7Hz), 2.48 (2H, t, J=7Hz), 2.50-2.61 (2H, m), 2.68 (3H, s), 2.61-2.74 (2H, m), 3.04-3.18 (2H, m), 4.33 (2H, t, J=7Hz), 6.00-6.08 (1H, m), 7.15-7.43 (6H, m), 7.59 (1H, d, J=2Hz), 7.81 (1H, s)

Example 3-4)

5-(2-Methylpropionamido)-7-methyl-1-[4-(4-phenyl-1,2,3,6-tetrahydro-1-pyridyl)butyl]benzimidazole

NMR ($CDCl_3$, δ) : 1.27 (6H, d, J=7Hz), 1.52-1.78 (2H, m), 1.81-2.03 (2H, m), 2.48 (2H, t, J=7Hz), 2.5-2.7 (5H, m), 2.68 (3H, s), 3.04-3.18 (2H, m), 4.33 (2H, t, J=7Hz), 6.00-6.08 (1H, m), 7.15-7.43 (6H, m), 7.59 (1H, d, J=2Hz), 7.81 (1H, s)

Example 3-5)

5-Methoxyacetamido-7-methyl-1-[4-(4-phenyl-1,2,3,6-tetrahydro-1-pyridyl)butyl]benzimidazole

NMR ($CDCl_3$, δ) : 1.52-1.78 (2H, m), 1.81-2.03 (2H, m), 2.48 (2H, t, J=7Hz), 2.50-2.61 (2H, m), 2.68 (3H, s), 2.61-2.74 (2H, m), 3.04-3.18 (2H, m), 3.53 (3H, s), 4.05 (2H, s), 4.33 (2H, t, J=7Hz), 6.00-6.08 (1H, m), 7.15-7.43 (6H, m), 7.59 (1H, d, J=2Hz), 7.81 (1H, s), 8.27 (1H, br s)

Example 4)

5-Acetamido-7-methyl-1-[4-(4-phenyl-1,2,3,6-tetrahydro-1-pyridyl)butyl]benzimidazole (110 mg) was dissolved in a mixture of chloroform (2 ml) and methanol (2 ml), and 1N hydrogen chloride in methanol (1 ml) was added at 20°C. After evaporation of the solvent, the residue was dissolved in water and freeze-dried to give 5-acetamido-7-methyl-1-[4-(4-phenyl-1,2,3,6-tetrahydro-1-pyridyl)butyl]benzimidazole dihydrochloride (135 mg).

NMR (CD_3OD, δ) : 1.90-2.12 (4H, m), 2.18 (3H, s), 2.80 (3H, s), 2.85-3.06 (2H, m), 3.33-3.46 (2H, m), 3.71-3.94 (2H, m), 4.02-4.22 (1H, m), 4.73 (2H, t, J=6Hz), 6.13 (1H, br s), 7.24-7.54 (6H, m), 8.29 (1H, s), 9.46 (1H, s)

Example 5-1)

A mixture of 5-acetamido-1-(4-chlorobutyl)-benzimidazole (223 mg) 4-phenyl-1,2,3,6-tetrahydropyridine hydrochloride (181 mg), sodium iodide (138 mg) and potassium carbonate (348 mg) in dimethylformamide (4 ml) was heated at 80°C for 5 hours. After cooling to 20°C, the mixture was poured into a mixture of ethyl acetate and aqueous sodium bicarbonate. The organic layer was separated, washed with water and brine, dried over magnesium sulfate and evaporated. The residue was purified by column chromatography on silica gel (50 g) eluting with 5% methanol in chloroform to yield 5-acetamido-1-[4-(4-phenyl-1,2,3,6-tetrahydro-1-pyridyl)-butyl]benzimidazole (213 mg) as a pale yellow solid.

mp : 155°C

NMR ($CDCl_3$, δ) : 1.50-1.78 (2H, m), 1.88-2.06 (2H, m), 2.21 (3H, s), 2.49 (2H, t, J=7Hz), 2.53-2.61 (2H, m), 2.61-2.71 (2H, m), 3.06-3.16 (2H, m), 4.22 (2H, t, J=7Hz), 6.00-6.08 (1H, m), 7.18-7.46 (6H, m), 7.58 (1H, dd, J=10Hz, 2Hz), 7.79 (1H, d, J=2Hz), 7.90 (1H, s)

The following compounds were obtained in substantially the same manner as that of Example 5-1).

Example 5-2)

1-[4-(4-Phenyl-1,2,3,6-tetrahydro-1-pyridyl)butyl]-5-propionamidobenzimidazole

mp : 123-124°C

NMR ($CDCl_3$, δ) : 1.28 (3H, t, J=7Hz), 1.50-1.70 (2H, m), 1.88-2.08 (2H, m), 2.35-2.70 (8H, m), 3.05-3.18 (2H, m), 4.20 (2H, t, J=7Hz), 6.00-6.09 (1H, m), 7.15-7.43 (6H, m), 7.58 (1H, dd, J=9Hz, 2Hz), 7.80 (1H, d, J=1Hz), 7.89 (1H, s)

Example 5-3)

5-Butyramido-1-[4-(4-phenyl-1,2,3,6-tetrahydro-1-pyridyl)butyl]benzimidazole

mp : 113-114°C

NMR ($CDCl_3$, δ) : 1.00 (3H, s, J=7Hz), 1.48-2.04 (6H, m), 2.26-2.71 (8H, m), 3.04-3.15 (2H, m), 4.18 (2H, t, J=7Hz), 6.00-6.08 (1H, m), 7.17-7.45 (6H, m), 7.62 (1H, dd, J=9Hz, 2Hz), 7.81 (1H, d, J=2Hz), 7.88 (1H, s)

Example 5-4)

5-(2-Methylpropionamido)-1-[4-(4-phenyl-1,2,3,6-tetrahydro-1-pyridyl)butyl]benzimidazole

mp : 137°C

NMR ($CDCl_3$, δ) : 1.29 (6H, d, J=7Hz), 1.50-1.69 (2H, m), 1.87-2.07 (2H, m), 2.40-2.61 (5H, m), 2.61-2.71 (2H, m), 3.05-3.16 (2H, m), 4.21 (2H, t, J=7Hz), 6.00-6.08 (1H, m), 7.17-7.45 (6H, m), 7.61 (1H, dd, J=8Hz, 2Hz), 7.80 (1H, d, J=2Hz), 7.89 (1H, s)

Example 6-1)

A mixture of 4-acetamido-1-(4-chlorobutyl)-benzimidazole (176 mg), 4-phenyl-1,2,3,6-tetrahydropyridine hydrochloride (143 mg), sodium iodide (109 mg) and potassium carbonate (274 mg) in dimethylformamide (3 ml) was heated at 80°C for 5 hours. After cooling to 20°C, the mixture was poured into a mixture of ethyl acetate and aqueous sodium bicarbonate. The organic layer was separated, washed with water and brine, dried over magnesium sulfate and evaporated. The residue was purified by column chromatography on silica gel (50 g) eluting with 5% methanol in chloroform, and recrystallized from a mixture of ethyl acetate and isopropyl ether to yield 4-acetamido-1-[4-(4-phenyl-

1,2,3,6-tetrahydro-1-pyridyl)butyl]benzimidazole (120 mg) as a pale yellow solid.

mp : 94-95°C

NMR ($CDCl_3$, δ) : 1.51-1.70 (2H, m), 1.89-2.08 (2H, m), 2.29 (3H, s), 2.48 (2H, t, J=7Hz), 2.52-2.61 (2H, m), 2.61-2.71 (2H, m), 3.08-3.14 (2H, m), 4.22 (2H, t, J=7Hz), 6.01-6.08 (1H, m)

Example 6-2)

1-[4-(4-Phenyl-1,2,3,6-tetrahydro-1-pyridyl)butyl]-4-propionamidobenzimidazole was obtained in substantially the same manner as that of Example 6-1).

mp : 89-90°C

NMR ($CDCl_3$, δ) : 1.30 (3H, t, J=7Hz), 1.51-1.70 (2H, m), 1.89-2.09 (2H, m), 2.41-2.70 (4H, m), 3.08-3.17 (2H, m), 4.21 (2H, t, J=7Hz), 6.01-6.08 (1H, m), 7.12 (1H, dd, J=8Hz, 2Hz), 7.18-7.42 (6H, m), 7.82 (1H, s), 8.28 (1H, d, J=8Hz), 8.47 (1H, br s)

Example 7-1)

A mixture of phenoxyacetic acid (971 mg), 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (1.22 g) and 1-hydroxybenzotriazole (862 mg) in N,N-dimethylformamide (10 ml) was stirred at 20°C for 1 hour, and then a mixture of 5-amino-7-methyl-1-[4-(4-phenyl-1,2,3,6-tetrahydropyridin-1-yl)butyl]benzimidazole trihydrochloride (2.0 g) and N,N-diisopropyl-N-ethylamine (2.6 ml) in N,N-dimethylformamide (10 ml) was added. After stirring at 20°C for 3 hours, the reaction mixture was partitioned between ethyl acetate and aqueous sodium bicarbonate. The organic layer was separated, washed with water and brine, and dried over magnesium sulfate. After evaporation of the solvent, the residue was purified by

column chromatography on silica gel (100 g) eluting with 5%-10% methanol in chloroform and by recrystallization from a mixture of ethanol and hexane to give 7-methyl-5-(2-phenoxyacetamido)-1-[4-(4-phenyl-1,2,3,6-tetrahydropyridin-1-yl)butyl]benzimidazole (1.60 g) as colorless crystals.

mp : 163-165°C

NMR ($CDCl_3$, δ) : 1.52-1.73 (2H, m), 1.82-2.08 (2H, m), 2.48 (2H, t, J=7Hz), 2.53-2.60 (2H, m), 2.60-2.68 (2H, m), 2.70 (3H, s), 3.04-3.17 (2H, m), 4.36 (2H, t, J=7Hz), 4.63 (2H, s), 6.00-6.08 (1H, m), 6.96-7.13 (3H, m), 7.18-7.44 (7H, m), 7.78 (1H, d, J=2Hz), 7.84 (1H, s), 8.32 (1H, d, J=2Hz)

Example 7-2)

To a suspension of 5-amino-7-methyl-1-[4-(4-phenyl-1,2,3,6-tetrahydropyridin-1-yl)butyl]benzimidazole trihydrochloride (500 mg) were added 2,6-lutidine (0.43 ml) and phenoxyacetyl chloride (0.18 ml) at 20°C. After stirring at 20°C for 4 hours, the reaction mixture was partitioned between chloroform and aqueous sodium bicarbonate. The organic layer was separated, washed with water and brine, and dried over magnesium sulfate. After evaporation of the solvent, the residue was purified by column chromatography on silica gel (50 g) eluting with 3%-10% methanol in chloroform and by recrystallization from ethyl acetate to give 7-methyl-5-(2-phenoxyacetamido)-1-[4-(4-phenyl-1,2,3,6-tetrahydropyridin-1-yl)butyl]benzimidazole (399 mg) as colorless crystals.

mp : 163-165°C

The following compounds were obtained in substantially the same manner as that of Example 7-1).

Example 7-3)

5-[2-(4-Fluorophenoxy)acetamido]-7-methyl-1-[4-(4-phenyl-1,2,3,6-tetrahydropyridin-1-yl)butyl]benzimidazole

mp : 163-165°C

NMR ($CDCl_3$, δ) : 1.54-1.72 (2H, m), 1.85-2.02 (2H, m), 2.48 (2H, t, J=8Hz), 2.52-2.62 (2H, m), 2.62-2.70 (2H, m), 2.70 (3H, s), 3.08-3.17 (2H, m), 4.35 (2H, t, J=8Hz), 4.60 (2H, s), 6.0-6.08 (1H, m), 6.92-7.10 (4H, m), 7.20-7.42 (6H, m), 7.76 (1H, d, J=2Hz), 7.84 (1H, s), 8.26 (1H, s)

Example 7-4)

5-[2-(4-Bromophenoxy)acetamido]-7-methyl-1-[4-(4-phenyl-1,2,3,6-tetrahydropyridin-1-yl)butyl]benzimidazole

mp : 171-173°C (dec.)

NMR ($CDCl_3$, δ) : 1.55-1.71 (2H, m), 1.86-2.00 (2H, m), 2.49 (2H, t, J=7Hz), 2.52-2.60 (2H, m), 2.64-2.70 (2H, m), 2.70 (3H, s), 3.10-3.17 (2H, m), 4.38 (2H, t, J=7Hz), 4.61 (2H, s), 6.02-6.07 (1H, m), 6.87-6.95 (2H, m), 7.20-7.50 (7H, m), 7.77 (1H, d, J=2Hz), 7.84 (1H, s), 8.22 (1H, s)

Example 7-5)

5-[2-(4-Methoxyphenoxy)acetamido]-7-methyl-1-[4-(4-phenyl-1,2,3,6-tetrahydropyridin-1-yl)butyl]benzimidazole

mp : 149-150°C

NMR ($CDCl_3$, δ) : 1.55-1.70 (2H, m), 1.86-2.00 (2H, m), 2.48 (2H, t, J=8Hz), 2.52-2.62 (2H, m), 2.64-2.70 (2H, m), 2.70 (3H, s), 3.10-3.20 (2H, m), 3.79 (2H, s), 4.37 (2H, t, J=8Hz), 4.58 (2H, s), 6.06 (1H, t, J=2Hz), 6.94 (4H, A_2B_2, J=8Hz), 7.2-7.4 (7H, m), 7.76 (1H, s), 7.82 (1H, s), 8.30 (1H, s)

Example 7-6)

5-[2-(4-Cyanophenoxy)acetamido]-7-methyl-1-[4-(4-phenyl-1,2,3,6-tetrahydropyridin-1-yl)butyl]benzimidazole

mp : 143-145°C

NMR ($CDCl_3$, δ) : 1.58-1.70 (2H, m), 1.87-2.00 (2H, m), 2.49 (2H, t, J=7Hz), 2.52-2.60 (2H, m), 2.65-2.70 (2H, m), 2.68 (3H, s), 3.10-3.17 (2H, m), 4.36 (2H, t, J=7Hz), 4.68 (2H, s), 6.03-6.10 (1H, m), 7.06-7.13 (2H, m), 7.21-7.40 (5H, m), 7.65-7.70 (2H, m), 7.75 (1H, s), 7.85 (1H, s), 8.21 (1H, s)

Example 7-7)

7-Methyl-1-[4-(4-phenyl-1,2,3,6-tetrahydropyridin-1-yl)butyl]-5-[2-{4-(trifluoromethyl)phenoxy}acetamido]-benzimidazole

NMR ($CDCl_3$, δ) : 1.58-1.75 (2H, m), 1.86-2.02 (2H, m), 2.50 (2H, t, J=7Hz), 2.67-2.70 (2H, m), 2.70 (3H, s), 3.10-3.20 (2H, m), 4.37 (2H, t, J=7Hz), 4.70 (2H, s), 6.04 (1H, t, J=1Hz), 7.10 (2H, d, J=10Hz), 7.18-7.40 (6H, m), 7.64 (2H, d, J=10Hz), 7.77 (1H, d, J=1Hz), 7.85 (1H, s), 8.24 (1H, s)

Example 7-8)

5-[2-(3,4-Dichlorophenoxy)acetamido]-7-methyl-1-[4-(4-phenyl-1,2,3,6-tetrahydropyridin-1-yl)butyl]benzimidazole

mp : 163-164°C (dec.)

NMR (DMSO-d_6, δ) : 1.48 (2H, m), 1.78 (2H, m), 2.3-2.6 (6H, m), 2.64 (3H, s), 3.03 (2H, d, J=3Hz), 4.36 (2H, t, J=8Hz), 4.76 (2H, s), 6.12 (1H, t, J=2Hz), 7.06 (1H, dd, J=3Hz, 10Hz), 7.1-7.5 (7H, m), 7.58 (1H, d, J=10Hz), 7.84 (1H, d, J=2Hz), 8.13 (1H, s), 9.99 (1H, s)

Example 7-9)

7-Methyl-5-[2-(4-methylphenoxy)acetamido]-1-[4-(4-phenyl-1,2,3,6-tetrahydropyridin-1-yl)butyl]benzimidazole

mp : 154-156°C (dec.)

NMR ($CDCl_3$, δ) : 1.56-1.73 (2H, m), 1.85-2.00 (2H, m), 2.31 (3H, s), 2.48 (2H, t, J=7Hz), 2.52-2.60 (2H, m), 2.65-2.70 (2H, m), 2.69 (3H, s), 3.10-3.15 (2H, m), 4.37 (2H, t, J=7Hz), 4.61 (2H, s), 6.02-6.07 (1H, m), 6.88-6.95 (2H, m), 7.13-7.41 (7H, m), 7.76 (1H, d, J=2Hz), 7.84 (1H, s), 8.30 (1H, s)

Example 7-10)

7-Methyl-5-[2-(3-methylphenoxy)acetamido]-1-[4-(4-phenyl-1,2,3,6-tetrahydropyridin-1-yl)butyl]benzimidazole

mp : 119-121°C

NMR ($CDCl_3$, δ) : 1.56-1.73 (2H, m), 1.86-2.00 (2H, m), 2.37 (3H, s), 2.49 (2H, t, J=7Hz), 2.52-2.60 (2H, m), 2.64-2.69 (2H, m), 2.70 (3H, s), 3.10-3.15 (2H, m), 4.37 (2H, t, J=7Hz), 4.62 (2H, s), 6.02-6.08 (1H, m), 6.78-6.90 (3H, m), 7.19-7.41 (6H, m), 7.78 (1H, d, J=2Hz), 7.83 (1H, s), 8.30 (1H, s)

Example 7-11)

5-[2-(2-Methoxyphenoxy)acetamido]-7-methyl-1-[4-(4-phenyl-1,2,3,6-tetrahydropyridin-1-yl)butyl]benzimidazole

mp : 100-103°C

NMR ($CDCl_3$, δ) : 1.56-1.70 (2H, m), 1.85-2.00 (2H, m), 2.49 (2H, t, J=7Hz), 2.52-2.62 (2H, m), 2.64-2.69 (2H, m), 2.70 (3H, s), 3.09-3.17 (2H, m), 3.97 (3H, m), 4.37 (2H, t, J=7Hz), 4.69 (2H, s), 6.02-6.07 (1H, m), 6.92-7.11 (4H, m), 7.23-7.44 (5H, m), 7.70 (1H, d, J=2Hz), 7.83 (1H, s), 8.98 (1H, s)

Example 8-1)

7-Methyl-5-(2-phenoxyacetamido)-1-[4-(4-phenyl-1,2,3,6-tetrahydropyridin-1-yl)butyl]benzimidazole dihydrochloride was obtained in substantially the same manner as that of Example 4.

NMR (CD_3OD, δ) : 1.9-2.2 (4H, m), 2.7-3.1 (3H, m), 2.83 (3H, s), 3.3-3.5 (2H, m), 3.7-3.9 (2H, m), 4.0-4.2 (1H, m), 4.73 (2H, s), 4.77 (2H, t, J=8Hz), 6.15 (1H, t, J=2Hz), 6.9-7.1 (3H, m), 7.2-7.6 (8H, m), 8.34 (1H, s), 9.48 (1H, s)

Example 8-2)

5-[2-(4-Methoxyphenoxy)acetamido]-7-methyl-1-[4-(4-phenyl-1,2,3,6-tetrahydropyridin-1-yl)butyl]benzimidazole dihydrochloride was obtained in substantially the same manner as that of Example 4.

NMR (CD_3OD, δ) : 1.93-2.25 (4H, m), 2.84 (3H, s), 2.86-3.06 (2H, m), 3.30-3.48 (3H, m), 3.74 (3H, s), 3.75-3.95 (2H, m), 4.06-4.22 (1H, m), 4.66 (2H, s), 4.75 (2H, t, J=8Hz), 6.10-6.18 (1H, m), 6.94 (4H, A_2B_2, J=10Hz), 7.30-7.54 (6H, m), 8.35 (1H, d, J=2Hz), 9.50 (1H, s)

The following compounds were obtained in substantially the same manner as that of Example 7-1).

Example 9-1)

5-Cyclopentanecarboxamido-7-methyl-1-[4-(4-phenyl-1,2,3,6-tetrahydropyridin-1-yl)butyl]benzimidazole

mp : 182-183°C

NMR ($CDCl_3$, δ) : 1.50-2.06 (12H, m), 2.48 (2H, t, J=7Hz), 2.53-2.62 (2H, m), 2.62-2.73 (2H, m), 2.66 (3H, s), 3.07-3.18 (2H, m), 4.34 (2H, t, J=7Hz), 6.00-6.08 (1H, m), 7.18-7.47 (7H, m), 7.58 (1H, d, J=2Hz), 7.80 (1H, s)

Example 9-2)

5-(2-Cyclopentylacetamido)-7-methyl-1-[4-(4-phenyl-1,2,3,6-tetrahydropyridin-1-yl)butyl]benzimidazole

mp : 130-132°C

NMR ($CDCl_3$, δ) : 1.09-1.37 (2H, m), 1.47-1.74 (6H, m), 1.76-2.01 (4H, m), 2.25-2.42 (3H, m), 2.50 (2H, t, J=7Hz), 2.54-2.62 (2H, m), 2.62-2.75 (2H, m), 2.68 (3H, s), 3.08-3.18 (2H, m), 4.34 (2H, t, J=7Hz), 6.00-6.10 (1H, m), 7.17-7.46 (6H, m), 7.58 (1H, d, J=2Hz), 7.82 (1H, s)

The following compounds were obtained in substantially the same manner as that of Example 7-2).

Example 9-3)

5-Acrylamido-7-methyl-1-[4-(4-phenyl-1,2,3,6-tetrahydropyridin-1-yl)butyl]benzimidazole

mp : 161-162°C

NMR ($CDCl_3$, δ) : 1.54-1.76 (2H, m), 1.83-2.03 (2H, m), 2.50 (2H, t, J=7Hz), 2.54-2.63 (2H, m), 2.63-2.71 (2H, m), 2.69 (3H, s), 3.08-3.18 (2H, m), 4.36 (2H, t, J=7Hz), 5.78 (1H, dd, J=10Hz, 2Hz), 6.00-6.10 (1H, m), 6.27 (1H, dd, J=16Hz, 10Hz), 6.45 (1H, dd, J=16Hz, 2Hz), 7.18-7.54 (6H, m), 7.68 (1H, d, J=2Hz), 7.83 (1H, s)

Example 9-4)

5-Crotonamido-7-methyl-1-[4-(4-phenyl-1,2,3,6-tetrahydropyridin-1-yl)butyl]benzimidazole

mp : 154-155°C

NMR ($CDCl_3$, δ) : 1.53-1.70 (2H, m), 1.75-2.00 (2H, m), 1.90 (3H, d, J=8Hz), 2.49 (2H, t, J=8Hz), 2.55 (2H, t, J=5Hz), 2.65 (2H, t, J=5Hz), 2.68 (3H, s), 3.15 (2H, d, J=5Hz), 4.32 (2H, t, J=8Hz), 5.98 (1H, d, J=15Hz), 6.02 (1H, t,

J=5Hz), 6.90-7.08 (1H, m), 7.20-7.45 (6H, m), 7.65 (1H, s), 7.80 (1H, s)

Example 9-5)

5-Methacrylamido-7-methyl-1-[4-(4-phenyl-1,2,3,6-tetrahydropyridin-1-yl)butyl]benzimidazole

mp : 126-127°C

NMR (CD_3OD, δ) : 1.70-2.05 (4H, m), 2.70-3.35 (4H, m), 3.00 (3H, s), 3.28 (2H, t, J=8Hz), 3.55-3.90 (7H, m), 4.10 (2H, t, J=8Hz), 6.05 (1H, t, J=3Hz), 7.03-7.45 (6H, m), 7.60 (1H, s), 8.12 (1H, d, J=8Hz)

Example 9-6)

5-(Cinnamamido)-7-methyl-1-[4-(4-phenyl-1,2,3,6-tetrahydropyridin-1-yl)butyl]benzimidazole

mp : 164-165°C

NMR ($CDCl_3$, δ) : 1.54-1.77 (2H, m), 1.82-2.05 (2H, m), 2.49 (2H, t, J=7Hz), 2.55-2.63 (2H, m), 2.63-2.68 (2H, m), 2.70 (3H, s), 3.08-3.18 (2H, m), 4.36 (2H, t, J=7Hz), 6.01-6.09 (1H, m), 6.59 (1H, d, J=16Hz), 7.17-7.45 (5H, m), 7.45-7.61 (4H, m), 7.68-7.89 (3H, m)

The following compounds were obtained in substantially the same manner as that of Example 7-1).

Example 9-7)

5-(2-Methoxybenzamido)-7-methyl-1-[4-(4-phenyl-1,2,3,6-tetrahydropyridin-1-yl)butyl]benzimidazole

mp : 127°C

NMR ($CDCl_3$, δ) : 1.54-1.74 (2H, m), 1.83-2.04 (2H, m), 2.48 (2H, t, J=7Hz), 2.53-2.61 (2H, m), 2.61-2.69 (2H, m), 2.72 (3H, s), 3.08-3.18 (2H, m), 4.08 (3H, s)

Example 9-8)

7-Methyl-1-[4-(4-phenyl-1,2,3,6-tetrahydropyridin-1-yl)butyl]-5-(2-pyrazinecarboxamido)benzimidazole

mp : 184-187°C

NMR (DMSO-d_6, δ) : 1.70-2.00 (4H, m), 2.7-2.9 (2H, m), 3.1-4.1 (6H, m), 4.48 (2H, t, J=8Hz), 6.20 (1H, broad s), 7.26-7.60 (6H, m), 8.12 (1H, d, J=2Hz), 8.36 (1H, s), 8.84 (1H, dd, J=1Hz, 3Hz), 8.96 (1H, d, J=3Hz), 9.33 (1H, d, J=1Hz)

Example 9-9)

7-Methyl-5-[2-(methylamino)acetamido]-1-[4-(4-phenyl-1,2,3,6-tetrahydropyridin-1-yl)butyl]benzimidazole

mp : 140°C

NMR ($CDCl_3$, δ) : 1.52-1.72 (2H, m), 1.83-2.02 (2H, m), 2.22 (3H, s), 2.49 (2H, t, J=7Hz), 2.53-2.62 (2H, m), 2.62-2.73 (2H, m), 2.69 (3H, s), 3.09-3.18 (2H, m), 3.37 (2H, s), 4.37 (2H, t, J=7Hz), 6.00-6.08 (1H, m), 7.18-7.42 (6H, m), 7.74 (1H, d, J=2Hz), 7.84 (1H, s), 8.73 (1H, br s)

Example 9-10)

7-Methyl-5-[2-(phenylamino)acetamido]-1-[4-(4-phenyl-1,2,3,6-tetrahydropyridin-1-yl)butyl]benzimidazole

mp : 140-141°C

NMR ($CDCl_3$, δ) : 1.51-1.71 (2H, m), 1.75-1.99 (2H, m), 2.47 (2H, t, J=7Hz), 2.52-2.61 (2H, m), 2.61-2.72 (2H, m), 2.66 (3H, s), 3.05-3.17 (2H, m), 3.80 (2H, s), 4.33 (2H, t, J=7Hz), 6.00-6.08 (1H, m), 7.15-7.42 (11H, m), 7.62 (1H, d, J=2Hz), 7.81 (1H, s), 8.62 (1H, br s)

Example 9-11)

7-Methyl-5-[2-(phenylamino)acetamido]-1-[4-(4-phenyl-1,2,3,6-tetrahydropyridin-1-yl)butyl]benzimidazole

mp : 144-146°C

NMR ($CDCl_3$, δ) : 1.52-1.72 (2H, m), 1.50-2.00 (2H, m), 2.48 (2H, t, J=7Hz), 2.52-2.60 (2H, m), 2.62-2.70 (2H, m), 2.68 (3H, s), 3.08-3.15 (2H, m), 3.94 (2H, d, J=5Hz), 4.35 (2H, t, J=7Hz), 4.36 (1H, t, J=5Hz), 6.00-6.10 (1H, m), 6.72 (2H, d, J=8Hz), 6.86 (1H, t, J=7Hz), 7.20-7.52 (8H, m), 7.71 (1H, d, J=2Hz), 7.80 (1H, s), 8.55 (1H, s)

The following compound was obtained in substantially the same manner as that of Example 7-2).

Example 9-12)

5-Cyclobutanecarboxamido-7-methyl-1-[4-(4-phenyl-1,2,3,6-tetrahydropyridin-1-yl)butyl]benzimidazole

mp : 171-173°C

NMR ($CDCl_3$, δ) : 1.55-1.71 (2H, m), 1.85-2.08 (4H, m), 2.10-2.60 (10H, m), 2.62 (3H, s), 3.10-3.25 (1H, m), 3.12 (2H, t, J=3Hz), 4.37 (2H, t, J=8Hz), 6.03 (1H, t, J=3Hz), 7.10 (1H, s), 7.18-7.38 (5H, m), 7.58 (1H, s), 7.80 (1H, s)

Example 10-1)

5-Benzamido-7-methyl-1-[4-(4-phenyl-1,2,3,6-tetrahydropyridin-1-yl)butyl]benzimidazole dihydrochloride was obtained in substantially the same manner as that of Example 7-2) followed by that of Example 4.

NMR (CD_3OD, δ) : 1.92-2.20 (4H, m), 2.82 (3H, s), 2.80-3.00 (2H, m), 3.40 (2H, t, J=8Hz), 3.70-4.20 (4H, m), 4.75 (2H, t, J=8Hz), 6.13 (1H, t, J=3Hz), 7.25-7.65 (9H, m), 7.95 (2H, d, J=8Hz), 8.45 (1H, s), 9.45 (1H, s)

The following compounds were obtained in

substantially the same manner as that of Example 10-1).

Example 10-2)

7-Methyl-5-(2-thenamido)-1-[4-(4-phenyl-1,2,3,6-tetrahydropyridin-1-yl)butyl]benzimidazole dihydrochloride

NMR (CD_3OD, δ) : 1.92-2.20 (4H, m), 2.80 (3H, s), 2.85-3.00 (2H, m), 3.39 (2H, t, J=8Hz), 3.70-4.20 (4H, m), 4.79 (2H, t, J=8Hz), 6.18 (1H, t, J=3Hz), 7.15-7.60 (7H, m), 7.78 (1H, d, J=5Hz), 7.97 (1H, d, J=5Hz), 8.35 (1H, s), 9.45 (1H, s)

Example 10-3)

5-(2-Furamido)-7-methyl-1-[4-(4-phenyl-1,2,3,6-tetrahydropyridin-1-yl)butyl]benzimidazole dihydrochloride

NMR (CD_3OD, δ) : 1.90-2.20 (4H, m), 2.78 (3H, s), 2.80-3.00 (2H, m), 3.25-3.45 (4H, m), 3.70-4.20 (4H, m), 4.75 (2H, t, J=8Hz), 6.15 (1H, t, J=3Hz), 7.28-7.60 (6H, m), 7.79 (1H, s), 8.37 (1H, s), 9.42 (1H, s)

The following compounds were obtained in substantially the same manner as that of Example 1.

Example 11-1)

7-Methyl-5-(4-morpholinecarboxamido)-1-[4-[4-phenyl-1,2,3,6-tetrahydropyridin-1-yl)butyl]benzimidazole

NMR ($CDCl_3$, δ) : 1.51-1.81 (2H, m), 1.81-2.03 (2H, m), 2.40-2.61 (2H, m), 2.61-2.74 (5H, m), 3.08-3.18 (2H, m), 3.45-3.57 (4H, m), 3.69-3.81 (4H, m), 4.34 (2H, t, J=7Hz), 6.01-6.10 (1H, m), 6.39 (1H, br s), 7.14-7.45 (7H, m), 7.79 (1H, s)

Example 11-2)

5-(3,3-Dimethylureido)-7-methyl-1-[4-(4-phenyl-1,2,3,6-tetrahydropyridin-1-yl)butyl]benzimidazole

NMR ($CDCl_3$, δ) : 1.53-1.72 (2H, m), 1.79-2.02 (2H, m), 2.41-2.61 (4H, m), 2.61-2.72 (5H, m), 3.04 (6H, s), 3.08-3.17 (2H, m), 4.33 (2H, t, J=7Hz), 6.00-6.07 (1H, m), 6.35 (1H, br s), 7.17-7.44 (7H, m), 7.79 (1H, s)

The following compounds were obtained in substantially the same manner as that of Example 11-2).

Example 12-1)

7-Methyl-5-(4-morpholinecarboxamido)-1-[4-(4-phenyl-1,2,3,6-tetrahydropyridin-1-yl)butyl]benzimidazole dihydrochloride

mp : 170-172°C

NMR (MeOH-d_4, δ) : 1.90-2.22 (4H, m), 2.80 (3H, s), 2.84-3.03 (2H, m), 3.34-3.45 (2H, m), 3.50-3.60 (4H, m), 3.67-3.76 (4H, m), 3.76-3.93 (2H, m), 4.01-4.21 (1H, m), 4.72 (2H, t, J=6Hz), 6.15 (1H, br s), 7.30-7.52 (6H, m), 7.94 (1H, d, J=2Hz), 9.39 (1H, s)

Example 12-2)

5-(3,3-Dimethylureido)-7-methyl-1-[4-(4-phenyl-1,2,3,6-tetrahydropyridin-1-yl)butyl]benzimidazole dihydrochloride

mp : 130-133°C

NMR (MeOH-d_4, δ) : 1.90-2.28 (4H, m), 2.80 (3H, s), 2.85-3.03 (2H, m), 3.04 (6H, s), 3.34-3.47 (2H, m), 3.73-3.93 (2H, m), 4.05-4.21 (1H, m), 4.72 (2H, t, J=7Hz), 6.15 (1H, br s), 7.26-7.55 (6H, m), 7.93 (1H, d, J=2Hz), 9.43 (1H, s)

Example 13-1)

A mixture of 1-(4-chlorobutyl)-4-(morpholinocarbonyl)benzimidazole (381 mg), 4-phenyl-

1,2,3,6-tetrahydropyridine hydrochloride (254 mg), sodium iodide (195 mg) and potassium carbonate (489 mg) in N,N-dimethylformamide (4 ml) was stirred at 80°C for 5 hours, and then partitioned between ethyl acetate and aqueous sodium bicarbonate. The organic layer was separated, washed with water and brine, and dried over magnesium sulfate. After the evaporation of solvent, the residue was purified by column chromatography on silica gel eluting with 10% methanol in chloroform to give 4-(morpholinocarbonyl)-1-[4-(4-phenyl-1,2,3,6-tetrahydro-1-pyridyl)butyl]benzimidazole (445 mg) as an oil.

NMR ($CDCl_3$, δ) : 1.52-1.70 (2H, m), 1.89-2.07 (2H, m), 2.50 (2H, t, J=7Hz), 2.53-2.61 (2H, m), 2.61-2.72 (2H, m), 3.07-3.16 (2H, m), 3.37 (2H, br t), 3.63 (2H, br t), 3.77-3.88 (2H, m), 3.88-4.00 (2H, m), 4.22 (2H, t, J=7Hz), 6.00-6.08 (1H, m), 7.18-7.52 (8H, m), 7.96 (1H, s)

Example 13-2)

To a solution of 4-(morpholinocarbonyl)-1-[4-(4-phenyl-1,2,3,6-tetrahydro-1-pyridyl)butyl]benzimidazole (100 mg) in methanol (2 ml) was added 0.65N solution of hydrogen chloride in methanol (1.4 ml) at room temperature. After the evaporation of solvent, the residue was freeze-dried to give 4-(morpholinocarbonyl)-1-[4-(4-phenyl-1,2,3,6-tetrahydro-1-pyridyl)butyl]-benzimidazole dihydrochloride (80 mg) as pale yellow powder.

mp : 150-153°C

NMR (CD_3OD, δ) : 1.92-2.24 (4H, m), 2.76-3.12 (4H, m), 3.32-3.47 (2H, m), 3.50-4.20 (12H, m), 4.70 (2H, t, J=7Hz), 6.12 (1H, broad s), 7.30-7.53 (5H, m), 7.69-7.84 (2H, m), 8.20 (1H, d, J=9Hz), 9.73 (1H, s)

Example 13-3)

To a solution of 4-(morpholinocarbonyl)-1-[4-(4-phenyl-1,2,3,6-tetrahydro-1-pyridyl)butyl]benzimidazole (200 mg) in tetrahydrofuran (7 ml) was added 1M solution of lithium aluminum hydride in tetrahydrofuran (0.58 ml) at 0°C. After stirring at 0°C for 1 hour, the reaction mixture was partitioned between aqueous potassium sodium tartrate and ethyl acetate. The organic layer was separated, washed with water and brine, and dried over magnesium sulfate. After the evaporation of solvent, the residue was purified by preparative thin layer chromatography on silica gel eluting with a mixture of ethyl acetate and triethylamine to give 4-(morpholinomethyl)-1-[4-(4-phenyl-1,2,3,6-tetrahydro-1-pyridyl)butyl]benzimidazole (51 mg) as an oil.

NMR ($CDCl_3$, δ) : 1.53-1.74 (2H, m), 1.80-2.08 (2H, m), 2.44-2.75 (10H, m), 3.08-3.18 (2H, m), 3.69-3.80 (4H, m), 4.04 (2H, s), 4.22 (2H, t, J=7Hz), 6.00-6.09 (1H, m), 7.19-7.41 (8H, m), 7.90 (1H, s)

Example 13-4)

4-(Morpholinomethyl)-1-[4-(4-phenyl-1,2,3,6-tetrahydro-1-pyridyl)butyl]benzimidazole trihydrochloride was obtained in substantially the same manner as that of Example 13-2).

mp : 130-135°C

NMR (MeOH-d_4, δ) : 1.84-2.07 (2H, m), 2.07-2.25 (2H, m), 2.75-3.10 (2H, m), 3.31-3.58 (6H, m), 3.70-4.20 (6H, m), 4.73 (2H, t, J=7Hz), 4.84 (2H, s), 6.12 (1H, br s), 7.25-7.53 (5H, m), 7.80 (1H, t, J=8Hz), 7.92 (1H, d, J=8Hz), 8.24 (1H, d, J=8Hz), 9.79 (1H, s)

Example 14-1)

1-[4-(4-Phenyl-1,2,3,6-tetrahydro-1-pyridyl)butyl]-4-(pyrrolidin-1-ylcarbonyl)benzimidazole was obtained in substantially the same manner as that of Example 13-1).

NMR ($CDCl_3$, δ) : 1.77-2.10 (4H, m), 2.49 (2H, t, J=7Hz), 2.53-2.61 (2H, m), 2.61-2.72 (2H, m), 3.05-3.16 (2H, m), 3.39 (2H, t, J=6Hz), 3.78 (2H, t, J=6Hz), 4.24 (2H, t, J=6Hz), 6.00-6.10 (1H, m), 7.18-7.50 (8H, m), 7.95 (1H, s)

Example 14-2)

1-[4-(4-Phenyl-1,2,3,6-tetrahydro-1-pyridyl)butyl]-4-(pyrrolidin-1-ylcarbonyl)benzimidazole dihydrochloride was obtained in substantially the same manner as that of Example 13-2).

mp : 62-63°C

NMR (MeOH-d_4, δ) : 1.84-2.26 (8H, m), 2.78-3.11 (2H, m), 3.34-3.48 (3H, m), 3.58 (2H, t, J=7Hz), 3.66-3.91 (4H, m), 4.03-4.20 (1H, m), 4.70 (2H, t, J=7Hz), 6.12 (1H, br s), 7.28-7.52 (5H, m), 7.79 (1H, t, J=8Hz), 7.88 (1H, d, J=8Hz), 8.20 (1H, d, J=8Hz), 9.70 (1H, s)

Example 14-3)

1-[4-(4-Phenyl-1,2,3,6-tetrahydro-1-pyridyl)butyl]-4-(pyrrolidin-1-ylmethyl)benzimidazole was obtained in substantially the same manner as that of Example 13-3).

NMR ($CDCl_3$, δ) : 1.53-1.72 (2H, m), 1.73-1.89 (4H, m), 1.89-2.06 (2H, m), 2.49 (2H, t, J=7Hz), 2.53-2.37 (8H, m), 3.06-3.18 (2H, m), 4.12-4.30 (4H, m), 6.01-6.10 (1H, m), 7.18-7.49 (8H, m), 7.91 (1H, s)

Example 14-4)

1-[4-(4-Phenyl-1,2,3,6-tetrahydro-1-pyridyl)butyl]-4-

(pyrrolidin-1-ylmethyl)benzimidazole trihydrochloride was obtained in substantially the same manner as that of Example 13-2).

mp : 95-97°C

NMR (MeOH-d_4, δ) : 1.86-2.35 (8H, m), 2.73-3.10 (2H, m), 3.33-3.46 (4H, m), 3.55-4.20 (6H, m), 4.70 (2H, t, J=7Hz), 4.90 (2H, s), 6.12 (1H, br s), 7.28-7.52 (5H, m), 7.80 (1H, t, J=8Hz), 7.94 (1H, d, J=8Hz), 8.21 (1H, d, J=8Hz), 9.79 (1H, s)

Example 15-1)

4-(4-Methylpiperazin-1-ylcarbonyl)-1-[4-(4-phenyl-1,2,3,6-tetrahydro-1-pyridyl)butyl]benzimidazole was obtained in substantially the same manner as that of Example 13-1).

NMR ($CDCl_3$, δ) : 1.50-1.75 (2H, m), 1.84-2.08 (2H, m), 2.31 (3H, s), 2.29-2.40 (2H, m), 2.41-2.61 (6H, m), 2.68 (2H, t, J=6Hz), 3.10-3.16 (2H, m), 3.46 (2H, t, J=5Hz), 3.93 (2H, t, J=5Hz), 4.23 (2H, t, J=5Hz), 6.07 (1H, s), 7.17-7.52 (8H, m), 7.93 (1H, s)

Example 15-2)

4-(4-Methylpiperazin-1-ylcarbonyl)-1-[4-(4-phenyl-1,2,3,6-tetrahydro-1-pyridyl)butyl]benzimidazole trihydrochloride was obtained in substantially the same manner as that of Example 13-2).

mp : 230-233°C

NMR ($CDCl_3$, δ) : 1.88-2.30 (4H, m), 2.80-3.08 (5H, m), 3.55-4.30 (8H, m), 6.16 (1H, s), 7.20-7.55 (4H, m), 7.60-7.90 (2H, m), 8.01 (1H, s), 8.40 (1H, s)

Example 16-1)

4-(N,N-Dimethylcarbamoyl)-1-[4-(4-phenyl-1,2,3,6-

tetrahydro-1-pyridyl)butyl]benzimidazole was obtained in substantially the same manner as that of Example 13-1).

NMR ($CDCl_3$, δ) : 1.51-1.71 (2H, m), 1.91-2.08 (2H, m), 2.49 (2H, t, J=8Hz), 2.53-2.61 (2H, m), 2.62-2.72 (2H, m), 2.96 (3H, s), 3.08-3.16 (2H, m), 3.22 (3H, s), 4.25 (2H, t, J=8Hz), 6.00-6.08 (1H, m), 7.18-7.52 (8H, m), 7.94 (1H, s)

Example 16-2)

4-(N,N-Dimethylcarbamoyl)-1-[4-(4-phenyl-1,2,3,6-tetrahydro-1-pyridyl)butyl]benzimidazole dihydrochloride was obtained in substantially the same manner as that of Example 13-2).

mp : 112-115°C

NMR (MeOH-d_4, δ) : 1.90-2.25 (4H, m), 2.75-3.01 (2H, m), 3.05 (3H, s), 3.19 (3H, s), 3.33-3.46 (3H, m), 3.73-3.93 (2H, m), 4.03-4.20 (1H, m), 4.70 (2H, t, J=7Hz), 6.13 (1H, br s), 7.22-7.42 (3H, m), 7.42-7.54 (2H, m), 7.69-7.81 (2H, m), 8.19 (1H, dd, J=8Hz, 2Hz), 9.72 (1H, s)

Example 16-3)

4-(N,N-Dimethylaminomethyl)-1-[4-(4-phenyl-1,2,3,6-tetrahydro-1-pyridyl)butyl]benzimidazole was obtained in substantially the same manner as that of Example 13-3).

NMR ($CDCl_3$, δ) : 1.52-1.70 (2H, m), 1.78-2.08 (2H, m), 2.38 (6H, s), 2.49 (2H, t, J=7Hz), 2.53-2.60 (2H, m), 2.61-2.70 (2H, m), 3.08-3.16 (2H, m), 4.00 (2H, s), 4.22 (2H, t, J=7Hz), 6.01-6.08 (1H, m), 7.18-7.42 (8H, m), 7.92 (1H, s)

Example 16-4)

4-(N,N-Dimethylaminomethyl)-1-[4-(4-phenyl-1,2,3,6-tetrahydro-1-pyridyl)butyl]benzimidazole trihydrochloride was obtained in substantially the same manner as that of

Example 13-2).

mp : 227-228°C

NMR (MeOH-d_4, δ) : 1.88-2.07 (2H, m), 2.07-2.55 (2H, m), 2.74-2.90 (2H, m), 2.96 (6H, s), 3.32-3.42 (3H, m), 3.70-3.90 (2H, m), 4.00-4.20 (1H, m), 4.69 (2H, t, J=7Hz), 4.82 (2H, s), 6.15 (1H, br s), 7.25-7.53 (5H, m), 7.72-7.90 (2H, m), 8.21 (1H, d, J=7Hz), 9.67 (1H, s)

Example 17

Isopropyl 1-[4-(4-phenyl-1,2,3,6-tetrahydro-1-pyridyl)butyl-4-benzimidazolecarboxylate was obtained in substantially the same manner as that of Example 13-1).

mp : 61°C

NMR ($CDCl_3$, δ) : 1.45 (6H, d, J=7Hz), 1.50-1.69 (2H, m), 1.88-2.06 (2H, m), 2.48 (2H, t, J=6Hz), 2.52-2.60 (2H, m), 2.61-2.70 (2H, m), 3.07-3.14 (2H, m), 4.27 (2H, t, J=6Hz), 5.28-5.45 (1H, m), 6.00-6.07 (1H, m), 7.18-7.40 (6H, m), 7.60 (1H, d, J=9Hz), 7.93 (1H, d, J=9Hz), 8.06 (1H, s)

Example 18

Ethyl 1-[4-(4-phenyl-1,2,3,6-tetrahydro-1-pyridyl)butyl]-4-benzimidazolecarboxylate was obtained in substantially the same manner as that of Example 13-1).

mp : 83-85°C

NMR ($CDCl_3$, δ) : 1.48 (3H, t, J=7Hz), 1.55-1.78 (2H, m), 1.90-2.08 (2H, m), 2.48 (2H, t, J=7Hz), 2.53-2.60 (2H, m), 2.61-2.69 (2H, m), 3.07-3.10 (2H, m), 4.27 (2H, t, J=7Hz), 4.55 (2H, q, J=7Hz), 6.06 (1H, s), 7.18-7.42 (7H, m), 7.62 (1H, d, J=8Hz), 7.99 (1H, d, J=8Hz), 8.08 (1H, s)

Example 19

To a solution of 5-acetamido-7-methyl-1-[4-(4-phenyl-1,2,3,6-tetrahydro-1-pyridyl)butyl]benzimidazole (200 mg) in 1,4-dioxane (10 ml) was added Lawesson's reagent (2,4-bis(4-methoxyphenyl)-1,3-dithia-2,4-diphosphetane-2,4-disulfide) (404 mg) at 20°C. The reaction mixture was heated at 100°C under stirring for 2.5 hours. And then it was poured into a mixture of ethyl acetate and aqueous sodium bicarbonate. The organic layer was separated, washed with water and brine and dried over magnesium sulfate. The residue was purified by column chromatography on silica gel (50 g) eluting with 5% methanol in chloroform to give 7-methyl-1-[4-(4-phenyl-1,2,3,6-tetrahydro-1-pyridyl)butyl]-5-thioacetamidobenzimidazole (40 mg) as a yellow solid.

mp : 126-127°C

NMR ($CDCl_3$, δ) : 1.54-1.75 (2H, m), 1.83-2.06 (2H, m), 2.49 (1.5H, s), 2.50-2.63 (4H, m), 2.63-2.74 (2H, m), 2.68 (3H, s), 2.76 (1.5H, s), 3.07-3.23 (2H, m), 4.29-4.47 (2H, q, J=7Hz), 5.98-6.08 (1H, m), 6.80 (0.5H, br s), 7.15-7.42 (6H, m), 7.72 (0.5H, br s), 7.85 (0.5H, s), 7.91 (0.5H, s), 9.38 (0.5H, br s), 9.72 (0.5H, br s)

Example 20

A mixture of 1-(4-chlorobutyl)-4-(phenylcarbamoyl)benzimidazole (150 mg), 4-phenyl-1,2,3,6-tetrahydropyridine hydrochloride (113 mg), sodium iodide (108 mg) and potassium carbonate (199 mg) in dimethylformamide (5 ml) was heated at 80°C for 5 hours. The mixture was partitioned between ethyl acetate and water. The organic layer was separated, washed with water and brine, dried over magnesium sulfate, and evaporated. The residue was purified by column chromatography on silica gel eluting with 2% methanol in chloroform to give

N-phenyl-1-[4-(4-phenyl-1,2,3,6-tetrahydro-1-pyridyl)butyl]-4-(phenylcarbamoyl)benzimidazole (161 mg) as colorless crystals.

mp : 135-140°C

NMR ($CDCl_3$, δ) : 1.57-1.70 (2H, m), 1.95-2.08 (2H, m), 2.50 (2H, t, J=7Hz), 2.56-2.60 (2H, m), 2.66 (2H, t, J=5Hz), 3.08-3.15 (2H, m), 4.29 (2H, t, J=7Hz), 6.00-6.08 (1H, m), 7.12 (1H, t, J=7Hz), 7.20-7.45 (9H, m), 7.62 (1H, dd, J=1, 7Hz), 7.91 (2H, d, J=7Hz), 8.02 (1H, s), 8.28 (1H, dd, J=1, 7Hz)

The following compounds were obtained in substantially the same manner as that of Example 20.

Example 21

1-[4-(4-Phenyl-1,2,3,6-tetrahydro-1-pyridyl)butyl]-4-(pyrazin-2-ylcarbamoyl)benzimidazole

NMR ($CDCl_3$, δ) : 1.58-1.70 (2H, m), 1.96-2.10 (2H, m), 2.52 (2H, t, J=7Hz), 2.55-2.60 (2H, m), 2.66 (2H, t, J=6Hz), 3.10-3.16 (2H, m), 4.32 (2H, t, J=7Hz), 6.02-6.08 (2H, m), 7.20-7.41 (5H, m), 7.46 (1H, t, J=8Hz), 7.68 (1H, d, J=8Hz), 8.10 (1H, s), 8.27 (1H, d, J=8Hz), 8.36 (1H, s), 8.38 (1H, s), 9.85 (1H, s)

Example 22

1-[4-(4-Phenyl-1,2,3,6-tetrahydro-1-pyridyl)butyl]-4-(pyrimidin-2-ylcarbamoyl)benzimidazole

mp : 141-142°C

NMR ($CDCl_3$, δ) : 1.63 (2H, quintet, J=7Hz), 2.02 (2H, quintet, J=7Hz), 2.50 (2H, t, J=7Hz), 2.54-2.60 (2H, m), 2.66 (2H, t, J=6Hz), 3.08-3.14 (2H, m), 4.32 (2H, t, J=7Hz), 6.03-6.08 (1H, m), 7.03 (1H, t, J=5Hz), 7.20-7.40 (5H, m), 7.45 (1H, t,

J=8Hz), 7.66 (1H, dd, J=1, 8Hz), 8.10 (1H, s), 8.34 (1H, dd, J=1, 8Hz), 8.63 (2H, d, J=5Hz)

Example 23

1-[4-(4-Phenyl-1,2,3,6-tetrahydro-1-pyridyl)butyl]-4-(pyrimidin-4-ylcarbamoyl)benzimidazole

NMR ($CDCl_3$, δ) : 1.63 (2H, quintet, J=7Hz), 2.03 (2H, quintet, J=7Hz), 2.50 (2H, t, J=7Hz), 2.54-2.62 (2H, m), 2.67 (2H, t, J=5Hz), 3.08-3.14 (2H, m), 4.33 (2H, t, J=7Hz), 6.04-6.07 (1H, m), 7.20-7.40 (5H, m), 7.06 (1H, t, J=8Hz), 7.69 (1H, dd, J=1, 8Hz), 8.12 (1H, s), 8.25 (1H, dd, J=1, 8Hz), 8.46 (1H, dd, J=1, 6Hz), 8.67 (1H, d, J=6Hz), 9.00 (1H, d, J=1Hz)

Example 24

1-[4-(4-Phenyl-1,2,3,6-tetrahydro-1-pyridyl)butyl]-4-(thiazol-2-ylcarbamoyl)benzimidazole

NMR ($CDCl_3$, δ) : 1.56-1.70 (2H, m), 1.98-2.10 (2H, m), 2.50 (2H, t, J=7Hz), 4.30 (2H, t, J=7Hz), 6.02-6.08 (1H, m), 7.00 (1H, d, J=4Hz), 7.20-7.40 (5H, m), 7.45 (1H, t, J=8Hz), 7.56 (1H, d, J=4Hz), 7.66 (1H, d, J=8Hz), 8.06 (1H, s), 8.25 (1H, d, J=5Hz)

Example 25

1-[4-(4-Phenyl-1,2,3,6-tetrahydro-1-pyridyl)butyl]-4-[(1,3,4-thiadiazol-2-yl)carbamoyl]benzimidazole

NMR ($CDCl_3$, δ) : 1.56-1.74 (2H, m), 2.00-2.12 (2H, m), 2.54 (2H, t, J=7Hz), 2.58-2.62 (2H, m), 2.68 (2H, t, J=5Hz), 3.10-3.18 (2H, m), 4.35 (2H, t, J=7Hz), 6.03-6.07 (1H, m), 7.20-7.43 (5H, m), 7.49 (1H, t, J=8Hz), 7.72 (1H, dd, J=1, 8Hz), 8.13 (1H, s), 8.26 (1H, dd, J=1, 8Hz), 8.89 (1H, s)

Example 26

1-[4-(4-Phenyl-1,2,3,6-tetrahydro-1-pyridyl)butyl]-4-[(2-thiazolin-2-yl)carbamoyl]benzimidazole

NMR ($CDCl_3$, δ) : 1.60 (2H, quintet, J=7Hz), 2.68 (2H, quintet, J=7Hz), 3.08-3.15 (2H, m), 3.34 (2H, t, J=9Hz), 4.08 (2H, t, J=9Hz), 4.28 (2H, t, J=7Hz), 6.02-6.08 (1H, m), 7.20-7.46 (6H, m), 7.65 (1H, dd, J=1, 8Hz), 8.02 (1H, s), 8.18 (1H, dd, J=1, 8Hz)

Example 27

4-(Cyclopropylcarbamoyl)-1-[4-(4-phenyl-1,2,3,6-tetrahydro-1-pyridyl)butyl]benzimidazole

NMR ($CDCl_3$, δ) : 0.70-0.78 (2H, m), 0.86-0.94 (2H, m), 1.55-1.67 (2H, m), 1.95-2.05 (2H, m), 2.50 (2H, t, J=7Hz), 2.54-2.62 (2H, m), 2.65-2.68 (2H, m), 3.02-3.15 (3H, m), 4.26 (2H, t, J=7Hz), 6.01-6.06 (1H, m), 7.20-7.42 (6H, m), 7.55 (1H, d, J=8Hz), 7.94 (1H, s), 8.19 (1H, d, J=8Hz), 9.90 (1H, d, J=2Hz)

Example 28

4-(Furfurylcarbamoyl)-1-[4-(4-phenyl-1,2,3,6-tetrahydro-1-pyridyl)butyl]benzimidazole

NMR ($CDCl_3$, δ) : 1.55-1.66 (2H, m), 1.92-2.04 (2H, m), 2.48 (2H, t, J=7Hz), 2.54-2.60 (2H, m), 2.65 (2H, t, J=6Hz), 3.08-3.14 (2H, m), 4.26 (2H, t, J=7Hz), 4.78 (2H, d, J=6Hz), 6.00-6.08 (1H, m), 6.32 (2H, s), 7.20-7.42 (7H, m), 7.56 (1H, d, J=8Hz), 7.96 (1H, s), 8.20 (1H, d, J=8Hz)

Example 29

4-(Morpholinocarbamoyl)-1-[4-(4-phenyl-1,2,3,6-tetrahydro-1-pyridyl)butyl]benzimidazole

NMR ($CDCl_3$, δ) : 1.62 (2H, quintet, J=7Hz),

1.99 (2H, quintet, J=7Hz), 2.49 (2H, t, J=7Hz), 2.55-2.62 (2H, m), 2.66 (2H, t, J=5Hz), 3.08-3.16 (6H, m), 3.92 (4H, t, J=5Hz), 4.28 (2H, t, J=7Hz), 6.04-6.08 (1H, m), 7.22-7.44 (6H, m), 7.57 (1H, dd, J=1, 8Hz), 7.98 (1H, s), 8.22 (1H, dd, J=1, 8Hz)

The following compounds were obtained in substantially the same manner as that of Example 7-1).

Example 30

5-(4-Methoxy-2-methylthio-5-pyridinecarboxamido)-7-methyl-1-[4-(4-phenyl-1,2,3,6-tetrahydro-1-pyridyl)butyl]benzimidazole

NMR ($CDCl_3$, δ) : 1.55-1.73 (2H, m), 1.85-2.07 (2H, m), 2.50 (2H, t, J=7Hz), 2.53-2.62 (2H, m), 2.63 (3H, d, J=2Hz), 2.65-2.75 (5H, m), 3.08-3.20 (2H, m), 4.25 (3H, s), 4.39 (2H, t, J=7Hz), 5.99-6.10 (1H, m), 7.18-7.44 (5H, m), 7.46 (1H, s), 7.77 (1H, s), 7.85 (1H, s), 9.20 (1H, s), 9.25 (1H, s)

Example 31

5-(4,5-Dibromo-2-thiophenecarboxamido)-7-methyl-1-[4-(4-phenyl-1,2,3,6-tetrahydro-1-pyridyl)butyl]benzimidazole

NMR ($CDCl_3$, δ) : 1.57-1.70 (2H, m), 1.83-1.98 (2H, m), 2.47 (2H, t, J=7Hz), 2.50-2.60 (2H, m), 2.62-2.71 (5H, m), 3.08-3.15 (2H, m), 4.35 (2H, t, J=7Hz), 6.01-6.07 (1H, m), 7.20-7.46 (7H, m), 7.67 (1H, d, J=2Hz), 7.82 (1H, s), 8.01 (1H, s)

Example 32

7-Methyl-5-(1-methyl-2-pyrrolecarboxamido)-1-[4-(4-phenyl-1,2,3,6-tetrahydro-1-pyridyl)butyl]benzimidazole

NMR ($CDCl_3$, δ) : 1.57-1.69 (2H, m), 1.87-1.97 (2H,

m), 2.49 (2H, t, J=7Hz), 2.52-2.62 (2H, m), 2.64-2.70 (2H, m), 2.70 (3H, s), 3.10-3.15 (2H, m), 3.99 (3H, s), 4.37 (2H, t, J=7Hz), 6.02-6.07 (1H, m), 6.13-6.17 (1H, m), 6.70-6.73 (1H, m), 6.77-6.80 (1H, m)

Example 33

7-Methyl-1-[4-(4-phenyl-1,2,3,6-tetrahydro-1-pyridyl)butyl]-5-(4-pyrazolecarboxamido)benzimidazole

NMR ($CDCl_3$:CD_3OD = 9:1, δ) : 1.57-1.75 (2H, m), 1.84-2.00 (2H, m), 2.51 (2H, t, J=7Hz), 2.57-2.66 (2H, m), 2.71 (3H, s), 2.71-2.77 (2H, m), 3.15-3.20 (2H, m), 4.40 (2H, t, J=7Hz), 6.03-6.10 (1H, m), 7.20-7.43 (6H, m), 7.61 (2H, s), 7.88 (1H, s), 8.16 (2H, s)

Example 34

7-Methyl-5-(2-methyl-4-oxazolecarboxamido)-1-[4-(4-phenyl-1,2,3,6-tetrahydro-1-pyridyl)butyl]benzimidazole

NMR ($CDCl_3$, δ) : 1.55-1.70 (2H, m), 1.82-1.99 (2H, m), 2.99 (2H, t, J=7Hz), 2.52 (3H, s), 2.52-2.60 (2H, m), 2.67 (2H, t, J=7Hz), 2.70 (3H, s), 3.05-3.15 (2H, m), 4.36 (2H, t, J=7Hz), 6.00-6.08 (1H, m), 7.19-7.45 (6H, m), 7.82 (1H, d, J=2Hz), 7.87 (1H, d, J=2Hz), 8.18 (1H, s), 8.68 (1H, s)

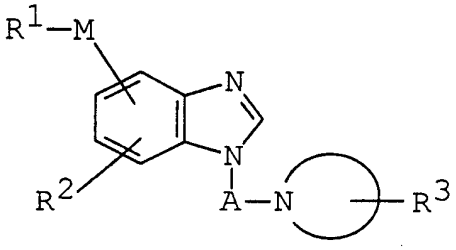
Example 35

5-(3,5-Dimethyl-4-isoxazolecarboxamido)-7-methyl-1-[4-(4-phenyl-1,2,3,6-tetrahydro-1-pyridyl)butyl]-benzimidazole

NMR ($CDCl_3$, δ) : 1.60-1.70 (2H, m), 1.80-2.00 (2H, m), 2.43-2.75 (15H, m), 3.10-3.16 (2H, m), 4.37 (2H, t, J=7Hz), 6.06 (1H, s), 7.20-7.41 (6H, m), 7.49 (1H, s), 7.64 (1H, s), 7.85 (1H, s)

CLAIM

1. A compound of the formula :

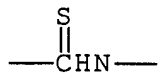


in which R^1 is lower alkoxy, optionally substituted lower alkyl, cyclo(lower)alkyl, optionally substituted lower alkenyl, mono- or di(lower)alkylamino, optionally substituted heterocyclic group, or optionally substituted aryl,

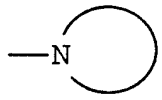
R^2 is hydrogen or lower alkyl,

R^3 is optionally substituted aryl,

A is lower alkylene,

M is -NHCO-, -CONH-,  , methylene or carbonyl, or

R^1-M is amino, and

the formula:  is N-containing heterocyclic group,

or pharmaceutically acceptable salts thereof.

2. The compound of Claim 1, wherein

R^1 is lower alkoxy, lower alkyl, lower alkoxy(lower)alkyl, C_6-C_{10} aryloxy(lower)alkyl optionally substituted by the group consisting of halogen, lower alkoxy, cyano, lower alkyl and

halo(lower)alkyl, cyclo(lower)alkyl(lower)alkyl, lower alkylthio(lower)alkyl, C_6-C_{10} arylthio(lower)alkyl, C_6-C_{10} arylamino(lower)alkyl, C_6-C_{10} aryl(lower)alkyl, heterocyclic-(lower)alkyl, cyclo(lower)alkyl, lower alkenyl, C_6-C_{10} aryl(lower)alkenyl, mono- or di(lower)alkylamino, heterocyclic group optionally substituted by the group consisting of halogen, lower alkoxy, cyano, lower alkyl, halo(lower)alkyl and lower alkylthio, C_6-C_{10} aryl optionally substituted by the group consisting of halogen, lower alkyl and lower alkoxy,

said heterocyclic group or heterocyclic moiety being

unsaturated 3 to 8-membered heteromonocyclic group containing 1 to 2 sulfur atom(s),

unsaturated 3 to 8-membered heteromonocyclic group containing 1 to 4 nitrogen atom(s),

saturated 3 to 8-membered heteromonocyclic group containing 1 to 4 nitrogen atom(s),

unsaturated condensed 7 to 12-membered heterocyclic group containing 1 to 4 nitrogen atom(s),

saturated condensed heterocyclic 7 to 12-membered group containing 1 to 4 nitrogen atom(s),

unsaturated 3 to 8-membered heteromonocyclic group containing 1 to 2 oxygen atom(s) and 1 to 3 nitrogen atom(s),

saturated 3 to 8-membered heteromonocyclic group containing 1 to 2 oxygen atom(s) and 1 to 3 nitrogen atom(s),

unsaturated condensed 7 to 12-membered heterocyclic group containing 1 to 2 oxygen atom(s) and 1 to 3 nitrogen atom(s),

unsaturated 3 to 8-membered heteromonocyclic

group containing 1 to 2 sulfur atom(s) and 1 to 3 nitrogen atom(s),

saturated 3 to 8-membered heteromonocyclic group containing 1 to 2 sulfur atom(s) and 1 to 3 nitrogen atom(s),

unsaturated condensed 7 to 12-membered heterocyclic group containing 1 to 2 sulfur atom(s) and 1 to 3 nitrogen atom(s),

unsaturated 3 to 8-membered heteromonocyclic group containing 1 to 2 oxygen atom(s),

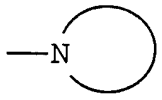
unsaturated 3 to 8-membered heteromonocyclic group containing an oxygen atom and 1 to 2 sulfur atom(s),

unsaturated condensed 7 to 12-membered heterocyclic group containing 1 to 2 sulfur atom(s), and

unsaturated condensed 7 to 12-membered heterocyclic group containing an oxygen atom and 1 to 2 sulfur atom(s),

R^3 is C_6-C_{10} aryl optionally substituted by the group consisting of halogen, lower alkyl and lower alkoxy,

R^1-M is amino, and

the formula:  is N-containing heterocyclic group attached to A at the ring nitrogen atom and is selected from the group consisting of

unsaturated 3 to 8-membered heteromonocyclic group containing 1 to 4 nitrogen atom(s),

saturated 3 to 8-membered heteromonocyclic group containing 1 to 4 nitrogen atom(s),

unsaturated 3 to 8-membered heteromonocyclic group containing 1 to 2 oxygen atom(s) and 1 to 3 nitrogen atom(s),

saturated 3 to 8-membered heteromonocyclic group containing 1 to 2 oxygen atom(s) and 1 to 3 nitrogen atom(s),

unsaturated 3 to 8-membered heteromonocyclic group containing 1 to 2 sulfur atom(s) and 1 to 3 nitrogen atom(s), and

saturated 3 to 8-membered heteromonocyclic group containing 1 to 2 sulfur atom(s) and 1 to 3 nitrogen atom(s).

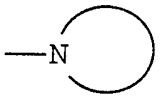
3. The compound of Claim 2, wherein

R^1 is lower alkoxy, lower alkyl, lower alkoxy(lower)alkyl, phenoxy(lower)alkyl, mono- or dihalophenoxy(lower)alkyl, lower alkoxyphenoxy(lower)alkyl, cyanophenoxy(lower)alkyl, lower alkylphenoxy(lower)alkyl, [trihalo(lower)alkyl]phenoxy(lower)alkyl, cyclo(lower)alkyl(lower)alkyl, lower alkylthio(lower)alkyl, phenylthio(lower)alkyl, C_6-phenylamino(lower)alkyl, phenyl(lower)alkyl, heterocyclic-(lower)alkyl, cyclo(lower)alkyl, lower alkenyl, phenyl(lower)alkenyl, mono- or di(lower)alkylamino, heterocyclic group optionally substituted by the group consisting of halogen, lower alkoxy, lower alkyl and halo(lower)alkyl, or phenyl optionally substituted by lower alkoxy, said heterocyclic group or heterocyclic moiety being selected from the group consisting of thienyl, azepinyl, pyrrolyl, pyrrolinyl, imidazolyl, pyrazolyl, pyridyl and its N-oxide, dihydropyridyl, pyrimidinyl, pyrazinyl, pyridazinyl, triazoly, tetrazolyl, perhydroazepinyl, pyrrolidinyl, imidazolidinyl, piperidino, piperazinyl, indolyl, isoindolyl, indolizinyl, benzimidazolyl, quinolyl,

isoquinolyl, indazolyl, benzotriazolyl, 7-azabicyclo[2.2.1]heptyl, 3-azabicyclo[3.2.2]-nonanyl, oxazolyl, isoxazolyl, oxadiazolyl, morpholinyl, sydnonyl, benzoxazolyl, benzoxadiazolyl, thiazolyl, isothiazolyl, thiadiazolyl, dihydrothiazinyl, thiazolidinyl, benzothiazolyl, benzothiadiazolyl, furyl, dihydroxathiinyl, benzothienyl, benzodithiinyl and benzoxathiinyl,

R^3 is phenyl optionally substituted by the group consisting of halogen, lower alkyl and lower alkoxy,

R^1-M is amino, and

the formula:  is N-containing heterocyclic group attached to A at the ring nitrogen atom and is selected from the group consisting of azepinyl, pyrrolyl, pyrrolinyl, imidazolyl, pyrazolyl, pyridyl and its N-oxide, dihydropyridyl, pyrimidinyl, pyrazinyl, pyridazinyl, triazolyl, tetrazolyl, perhydroazepinyl, pyrrolidinyl, imidazolidinyl, piperidino, piperazinyl, indolyl, isoindolyl, indolizinyl, benzimidazolyl, quinolyl, isoquinolyl, indazolyl, benzotriazolyl, 7-azabicyclo[2.2.1]heptyl, 3-azabicyclo[3.2.2]-nonanyl, oxazolyl, isoxazolyl, oxadiazolyl, morpholinyl, sydnonyl, benzoxazolyl, benzoxadiazolyl, thiazolyl, isothiazolyl, thiadiazolyl, dihydrothiazinyl, thiazolidinyl, benzothiazolyl and benzothiadiazolyl.

4. The compound of Claim 3, wherein

R^1 is lower alkoxy, lower alkyl, lower alkoxy(lower)alkyl, phenoxy(lower)alkyl, mono- or

dihalophenoxy(lower)alkyl, lower alkoxyphenoxy(lower)alkyl, cyanophenoxy(lower)alkyl, lower alkylphenoxy(lower)alkyl [trihalo(lower)alkyl]phenoxy(lower)alkyl, cyclo(lower)alkyl(lower)alkyl, lower alkylthio(lower)alkyl, phenylthio(lower)alkyl, phenylamino(lower)alkyl, phenyl(lower)alkyl, heterocyclic(lower)alkyl, cyclo(lower)alkyl, lower alkenyl, phenyl(lower)alkenyl, mono- or di(lower)alkylamino, heterocyclic group optionally substituted by the group consisting of halogen, lower alkoxy, lower alkyl and halo(lower)alkyl, or phenyl optionally substituted by lower alkoxy, said heterocyclic group or heterocyclic moiety being selected from the group consisting of thienyl, pyrrolyl, pyrazolyl, pyrimidinyl, pyrazinyl, pyrrolidinyl, piperidino, piperazinyl, oxazolyl, isoxazolyl, morpholinyl, thiazolyl, thiadiazolyl, thiazolinyl, benzothiazolyl, benzothiadiazolyl, furyl, dihydroxathiinyl, benzothienyl, benzodithiinyl and benzoxathiinyl,

R^1-M is amino, and

the formula :  is tetrahydropyridin-1-yl.

5. The compound of Claim 4, wherein

R^1-M is amino, lower alkanoylamino, lower alkanethioylamino, N,N-di(lower)alkylcarbamoylamino, lower alkoxycarbonylamino, lower alkenoylamino, cyclo(lower)alkanecarbonylamino, pyrazinylcarbonylamino, morpholinylcarbonylamino, furylcarbonylamino, thienylcarbonylamino optionally substituted by halogen, oxazolylcarbonylamino

optionally substituted by lower alkyl, isoxazolylcarbonylamino, optionally substituted by lower alkyl, pyrrolylcarbonylamino optionally substituted by lower alkyl, pyrazolylcarbonylamino, pyrimidinylcarbonylamino optionally substituted by the group consisting of lower alkoxy and lower alkylthio, lower alkoxy(lower)alkanoylamino, cyclo(lower)alkyl(lower)alkanoylamino, phenylamino(lower)alkanoylamino, phenoxy(lower)alkanoylamino, cyanophenoxy(lower)alkanoylamino, mono- or dihalophenoxy(lower)alkanoylamino, trihalo(lower)alkylphenoxy(lower)alkanoylamino, lower alkoxyphenoxy(lower)alkanoylamino, lower alkylphenoxy(lower)alkanoylamino, lower alkylthio(lower)alkanoylamino, phenylthio(lower)alkanoylamino, phenyl(lower)alkenoylamino, benzoylamino, lower alkoxybenzoylamino, morpholinocarbonyl, morpholinomethyl, pyrrolidinylcarbonyl, pyrrolidinylmethyl, piperazinylcarbonyl optionally substituted by lower alkyl, N,N-di(lower alkylcarbamoyl, N,N-di(lower)alkylaminomethyl, lower alkoxycarbonyl, piperidinocarbonyl, cyclo(lower)alkylcarbamoyl, phenylcarbamoyl, pyrazinylcarbamoyl, pyrimidinylcarbamoyl, thiazolylcarbamoyl, thiadiazolylcarbamoyl, dihydrothiazolylcarbamoyl, morpholinocarbamoyl, phenyl(lower)alkylcarbamoyl, furyl(lower)alkylcarbamoyl,

R^3 is phenyl, and

the formula  is 1,2,3,6-tetrahydropyridin-1-yl.

6. The compound of Claim 5, wherein

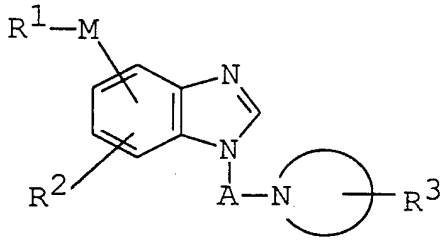
R^1-M is amino, C_1-C_4 alkanoylamino, C_1-C_4 alkanethioylamino, N,N-di(C_1-C_4)alkylcarbamoylamino, C_1-C_4 alkoxycarbonylamino, C_2-C_4 alkenoylamino, cyclo(C_1-C_4)alkanecarbonylamino, pyrazinylcarbonylamino, morpholinylcarbonylamino, furylcarbonylamino, thienylcarbonylamino, optionally substituted by halogen, oxazolylcarbonylamino optionally substituted by C_1-C_4 alkyl, isoxazolylcarbonylamino optionally substituted by C_1-C_4 alkyl, pyrrolylcarbonylamino optionally substituted by C_1-C_4 alkyl, pyrazolylcarbonylamino, pyrimidinylcarbonylamino optionally substituted by the group consisting of C_1-C_4 alkoxy and C_1-C_4 alkylthio, C_1-C_4 alkoxy(C_1-C_4)alkanoylamino, cyclo(C_1-C_4)alkyl(C_1-C_4)alkanoylamino, phenylamino(C_1-C_4)alkanoylamino, phenoxy(C_1-C_4)alkanoylamino, cyanophenoxy(C_1-C_4)alkanoylamino, mono- or dihalophenoxy(C_1-C_4)alkanoylamino, trihalo(C_1-C_4)alkylphenoxy(C_1-C_4)alkanoylamino, C_1-C_4 alkoxyphenoxy(C_1-C_4)alkanoylamino, C_1-C_4 alkylphenoxy(C_1-C_4)alkanoylamino, C_1-C_4 alkylthio(C_1-C_4)alkanoylamino, phenylthio(C_1-C_4)alkanoylamino, phenyl(C_2-C_4)alkenoylamino, benzoylamino, C_1-C_4 alkoxybenzoylamino, morpholinocarbonyl, morpholinomethyl, pyrrolidinylcarbonyl, pyrrolidinylmethyl, piperazinylcarbonyl optionally substituted by C_1-C_4 alkyl, N,N-di(C_1-C_4)alkylcarbamoyl, N,N-di(C_1-C_4)alkylaminomethyl, C_1-C_4 alkoxycarbonyl, piperidinocarbonyl, cyclo(C_1-C_4)alkylcarbamoyl, phenylcarbamoyl, pyrazinylcarbamoyl, pyrimidinylcarbamoyl, thiazolylcarbamoyl, thiadiazolylcarbamoyl, dihydrothiazolylcarbamoyl, morpholinocarbamoyl, phenyl(C_1-C_4)alkylcarbamoyl or

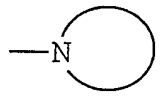
furyl(C_1-C_4)alkylcarbamoyl.

7. The compounds of Claims 1 to 6, wherein R^2 is hydrogen.

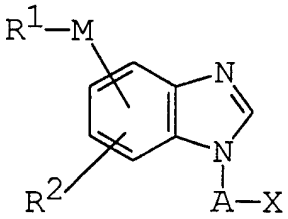
8. The compounds of Claims 1 to 6, wherein R^2 is lower or C_1-C_4 alkyl.

9. A process for the preparation of a compound of the formula :

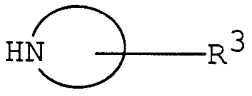


in which R^1, R^2, R^3, A, M and the formula :  are each as defined in claim 1, or salts thereof, which comprises

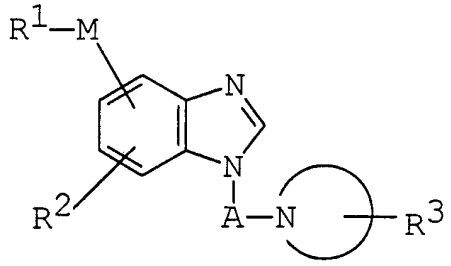
(a) reacting a compound of the formula :



or salts thereof, with a compound of the formula :

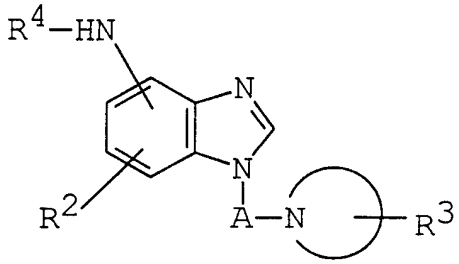


or salts thereof, to give a compound of the formula :

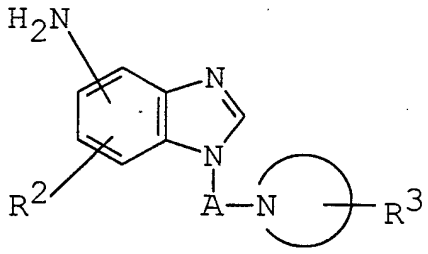


or salts thereof; or

(b) subjecting a compound of the formula :

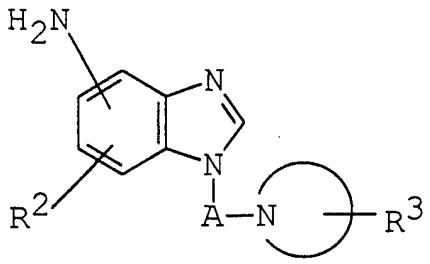


or salts thereof, to a removal reaction of common amino-protective group of R^4, to give a compound of the formula :

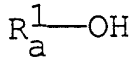


or salts thereof; or

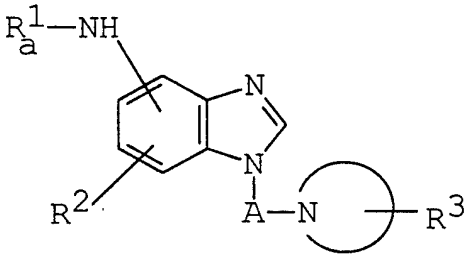
(c) reacting a compound of the formula :



or a reactive derivative at the amino group, or salts thereof, with a compound of the formula :

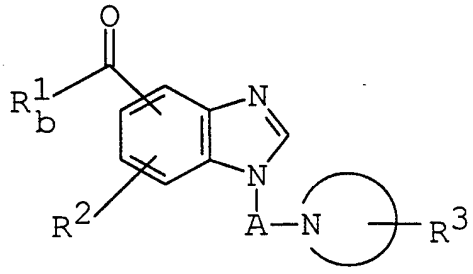


or a ractive derivative at the carboxy group, or salts thereof to give a compound of the formula :

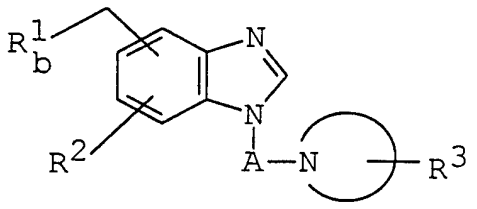


or salts thereof; or

(d) reducting the carbonyl group of a compound of the formula :

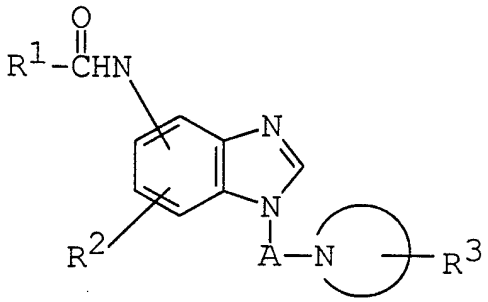


or salts thereof to give a compound of the formula :

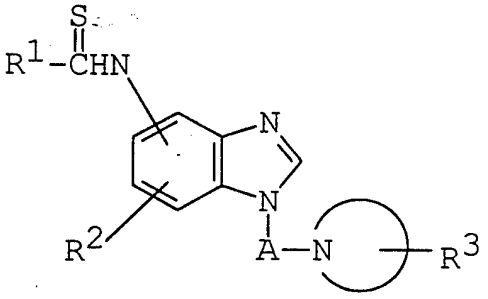


or a salts thereof; or

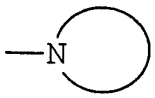
(e) reacting a compound of the formula :



or salts thereof with a Lawesson's reagent to give a compound of the formula :



or salts thereof;

in which R^1, R^2, R^3, A, M and the formula :  are each as defined above,

R^1_a is lower alkoxycarbonyl, lower alkanoyl, optionally substituted heterocyclic-carbonyl, mono- or

di(lower)alkylcarbamoyl, lower alkoxy(lower)alkanoyl, optionally substituted aryloxy(lower)alkanoyl, cyclo(lower)alkylcarbonyl, cyclo(lower)alkyl(lower)alkanoyl, lower alkenoyl, aryl(lower)alkenoyl, optionally substituted arylcarbonyl, lower alkylthio(lower)alkanoyl, arylthio(lower)alkanoyl or arylamino(lower)alkanoyl,

R_b^1 is optionally substituted heterocyclic group, mono- or di(lower)alkylamino, or lower alkoxy,

R^4 is common amino-protective group, and

X is a leaving group.

10. A pharmaceutical composition comprising, as an active ingredient, a compound of Claim 1 in admixture with a pharmaceutically acceptable carrier or excipient.

11. A compound of Claim 1 for use as a medicament.

12. Use of a compound of Claim 1 for the manufacture of a medicament for treating dopamine receptor mediated diseases, 5-HT receptor mediated diseases or α_1-receptor mediated diseases.

13. A method for the treatment of dopamine receptor mediated diseases, 5-HT receptor mediated diseases or α_1-receptor mediated diseases which comprises administering a compound of Claim 1 to a human being or an animal.

INTERNATIONAL SEARCH REPORT

International application No.
PCT/JP 94/01182

A. CLASSIFICATION OF SUBJECT MATTER
IPC 6 C07D401/06 A61K31/44 C07D401/14 C07D409/14 C07D405/14
C07D413/14 C07D417/14

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 6 C07D A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	EP,A,0 497 659 (LABORATORIOS DEL DR. ESTEVE, S.A.) 5 August 1992 ---	1-12
Y	EP,A,0 502 786 (LABORATORIOS DEL DR. ESTEVE, S.A.) 9 September 1992 ---	1-12
Y	EP,A,0 244 018 (AKZO N.V.) 4 November 1987 ---	1-12
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☐ Further documents are listed in the continuation of box C.

☒ Patent family members are listed in annex.

* Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

2

Date of the actual completion of the international search	Date of mailing of the international search report
8 November 1994	18 11. 94

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax (+31-70) 340-3016	Stellmach, J

Form PCT/ISA/210 (second sheet) (July 1992)

INTERNATIONAL SEARCH REPORT

International application No.
PCT/JP 94/01182

Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This international search report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. [X] Claims Nos.: 13
because they relate to subject matter not required to be searched by this Authority, namely:
Remark - Although claim 13 is directed to a method of treatment of human/animal body, the search has been carried out based on the alleged effects of the compounds.

2. [ ] Claims Nos.:
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:

3. [ ] Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. [ ] As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.

2. [ ] As all searchable claims could be searches without effort justifying an additional fee, this Authority did not invite payment of any additional fee.

3. [ ] As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:

4. [ ] No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

[ ] The additional search fees were accompanied by the applicant's protest.

[ ] No protest accompanied the payment of additional search fees.

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